The American Journal of

CARDIOLOGY

OFFICIAL JOURNAL OF THE American College of Cardiology

Call for Abstracts

Tenth Annual Meeting

May 17 to May 20, 1961

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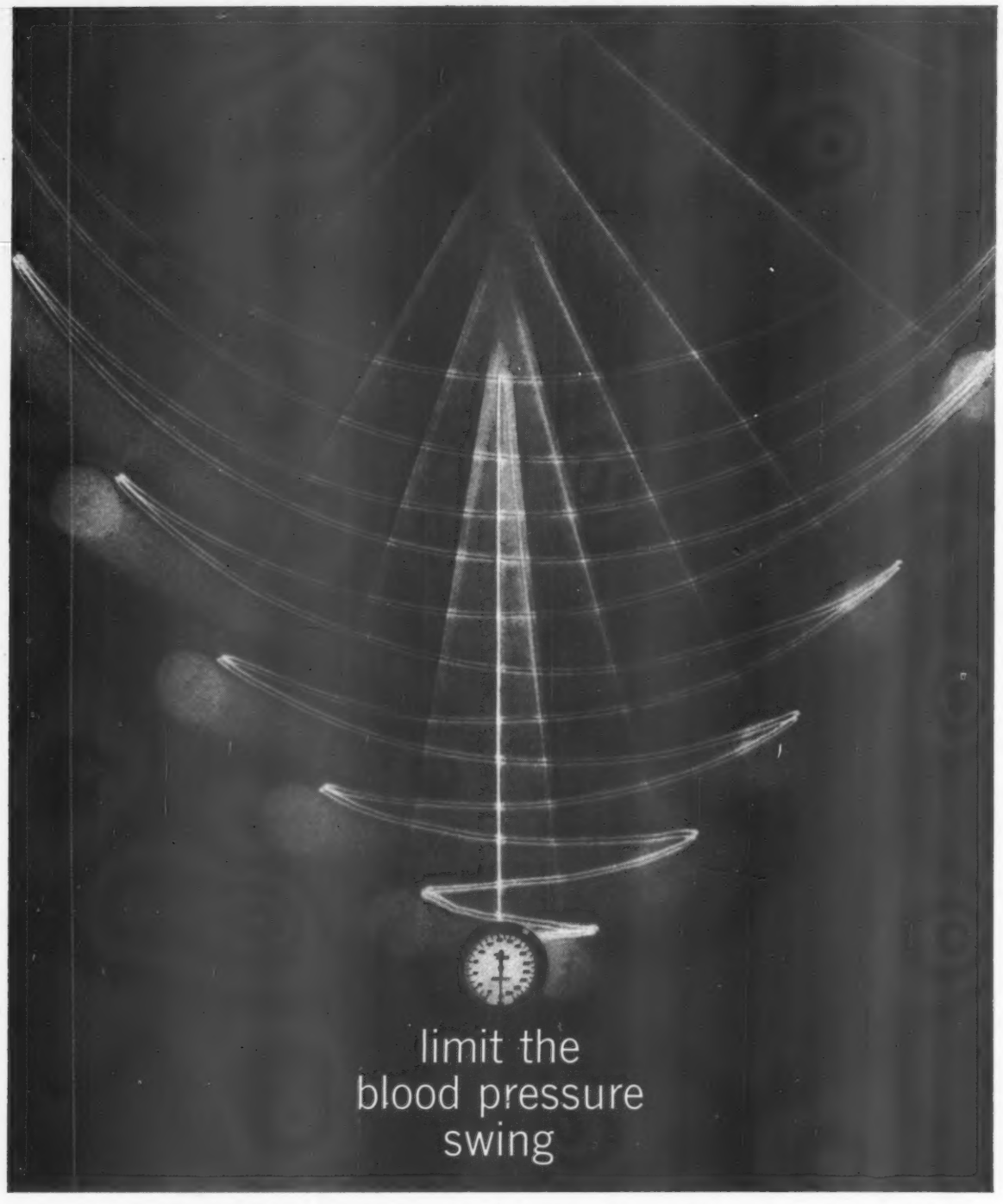
NOVEMBER 1960



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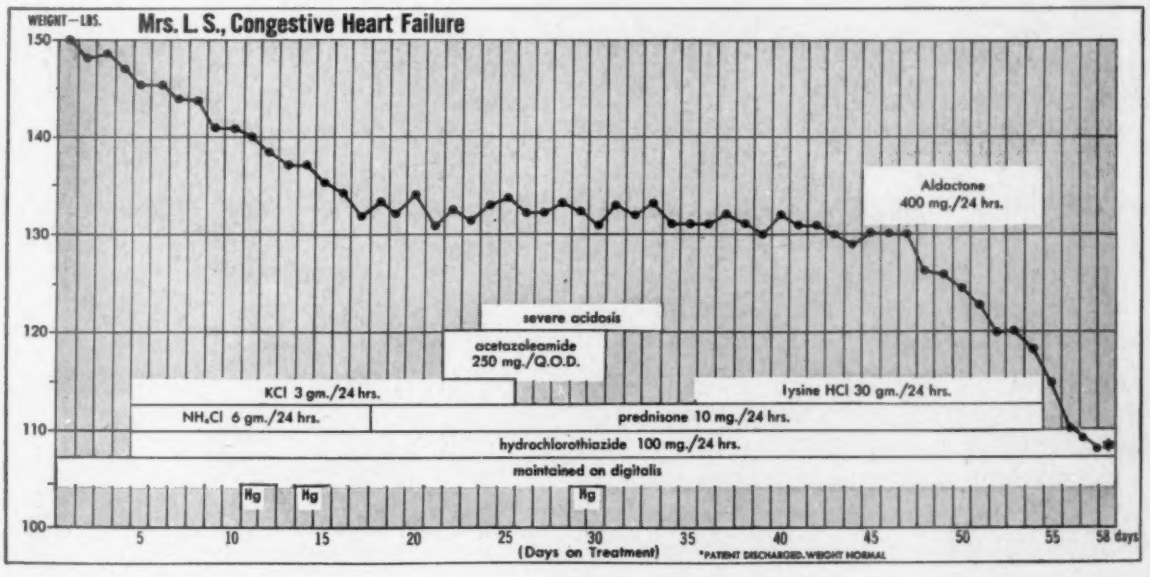

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References: **1.** Tandowsky, R. M.: Personal communication. **2.** Parsons, W. B.: *Curr. Therapeut. Res.* 2:137 (May) 1960. **3.** Thompson, C. E.: Personal communication. **4.** Biben, L. H.; Kurstin, W., and Protas, M.: Personal communication. **5.** Hobbs, T. G.: Personal communication.

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The American Journal of Cardiology

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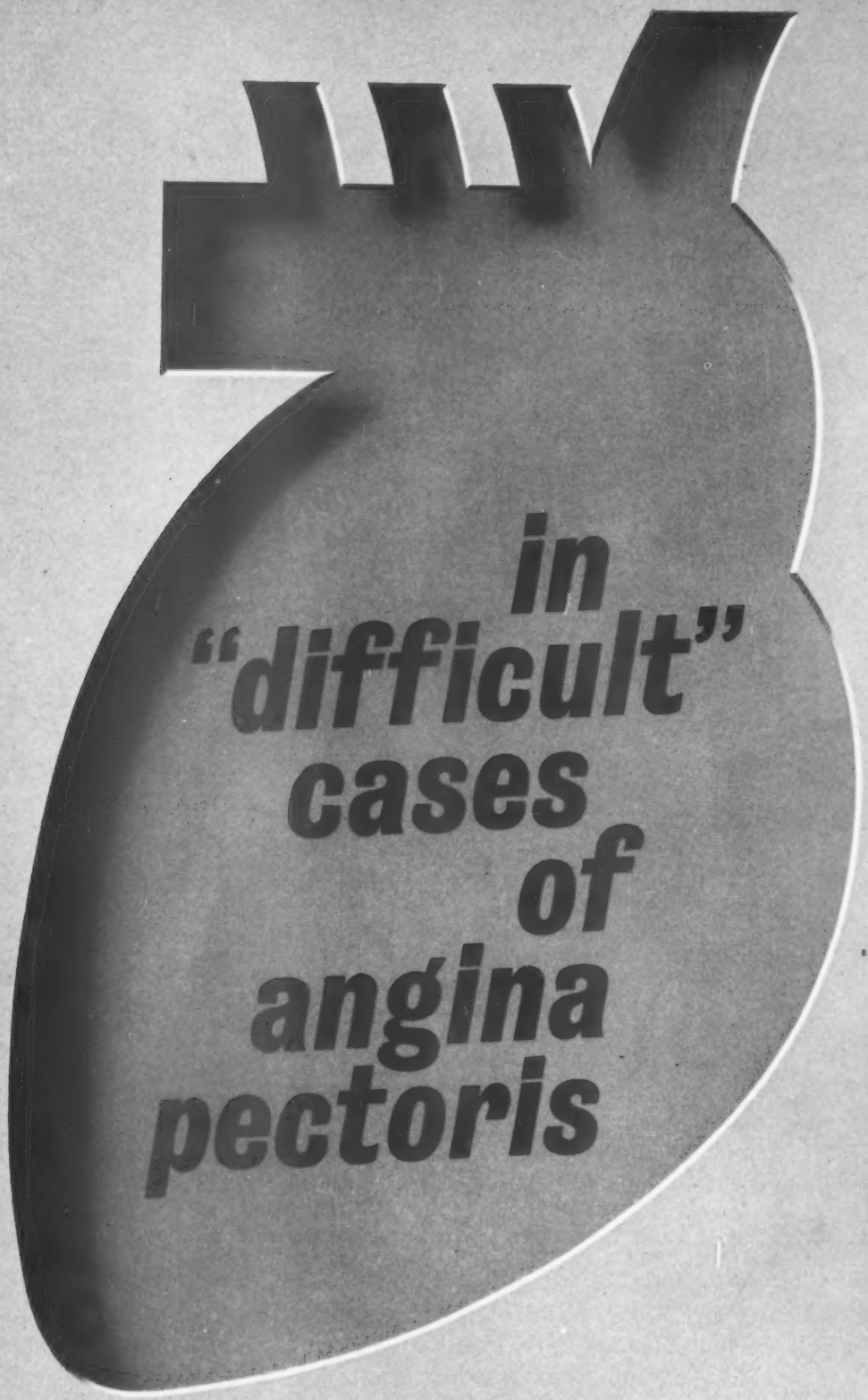

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Experimental Studies

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Report on Therapy

Case Reports

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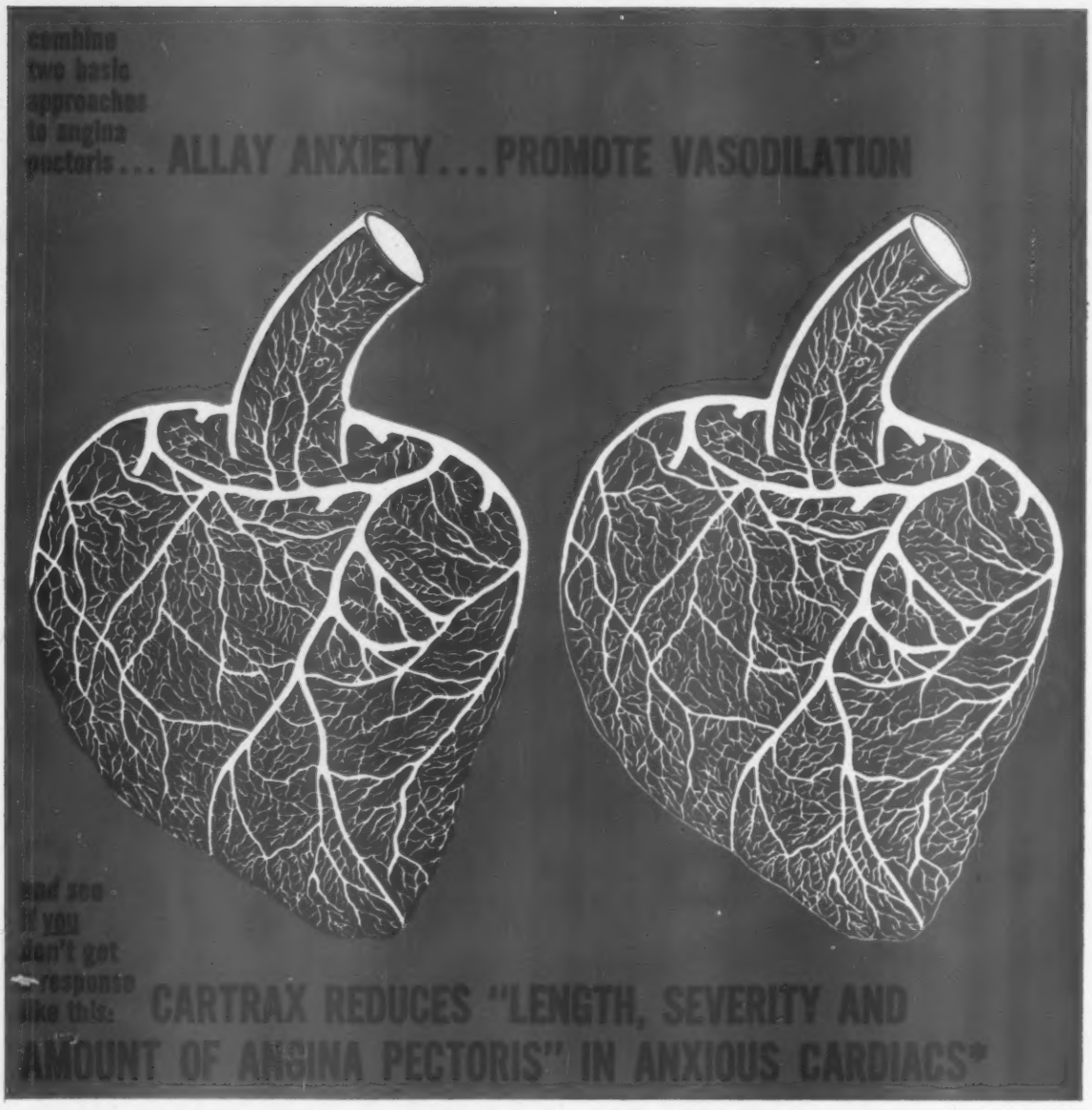

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*Coan, J. P., McAlpine, J. C., and Boone, J. A.: J. South Carolina M. A. 51:417 (Dec.) 1955.

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References: (1) Blaustein, A.: New York J. Med. *58*:701, 1958. (2) Lange, K., *et al.*: Am. Heart J. *55*:73, 1958. (3) Kellaway, G.: Brit. M. J. *2*:889, 1958. (4) Connell, W. E. and Mayer, G. A.: Canad. M.A.J. *80*:785, 1959. (5) Paul, H. V., Arscott, P. M., Koppel, J. L., and Olwin, J. H.: Surg. Gynec. & Obst. *108*:605, 1959.

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1. Blumberg, N. *et al.*: Fed. Proc. 17:351, March 1958. **2.** Boyd, L. J. *et al.*: Am. J. Cardiol. 3:229, Feb. 1959. **3.** Brick, H. *et al.*: J. Social Therapy 4:190, 1958. **4.** Bulla, J. D. *et al.*: Am. Pract. & Digest Treat. 10:1961, Nov. 1959. **5.** Ewing, J. A. and Haizlip, T. M.: Am. J. Psychiat. 114:835, March 1958. **6.** Friedman, A. P.: Ann. N. Y. Acad. Sc. 67:822, May 9, 1957. **7.** Greenberg, L. A. *et al.*: Ann. N. Y. Acad. Sc. 67:816, May 9, 1957. **8.** Holliday, A. R.: Northwest Med. 58:837, June 1959. **9.** Hollister, L. E. *et al.*: Dis. Nerv. System 17:289, Sept. 1956. **10.** Laird, D. M. *et al.*: Dis Nerv. System 18:346, Sept. 1957.

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11. Lasagna, L.: J. Chron. Dis. 3:122, Feb. 1956. 12. Muhlfelder, W. J. *et al.*: Dis. Nerv. System 20:587, Dec. 1959. 13. Pollak, M.: Practitioner 184:231, Feb. 1960. 14. Rickels, K. *et al.*: J.A.M.A. 171:1649, Nov. 21, 1959. 15. Russek, H. I.: Am. J. Cardiol. 3:547, April 1959. 16. Tucker, K. and Wilensky, H.: Am. J. Psychiat. 113:698, Feb. 1957.

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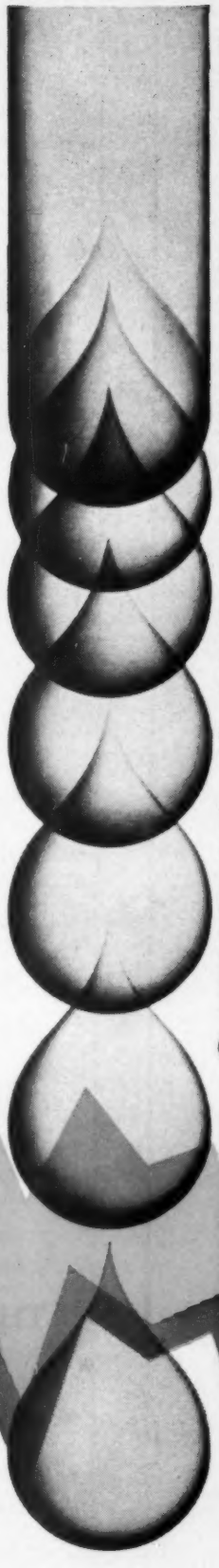

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(1) Stenger, E. G., et al.: Schweiz. med. Wchnschr. 89:1126, 1959. (2) Fuchs, M., Res: et al.: Current Therap. Research 2:11, January, 1960. (3) Ford, R. V.: Manuscript submitted for publication.

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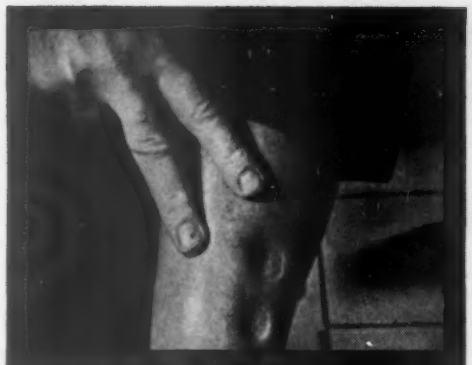

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1. Riseman, J.E.F., *et al.*: Circulation *17*:22 (Jan.) 1958.

2. Russek, H.I.: Circulation *18*:774 (Oct.) 1958.

3. Hirshleifer, I., *et al.*: Scientific Exhibit, A.M.A., Atlantic City, N. J., June, 1959.

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1. Selzer, A. and Rytand, D.A.: COUNCIL ON DRUGS, Report to Council J.A.M.A. 168:762, (Oct. 11) 1958.

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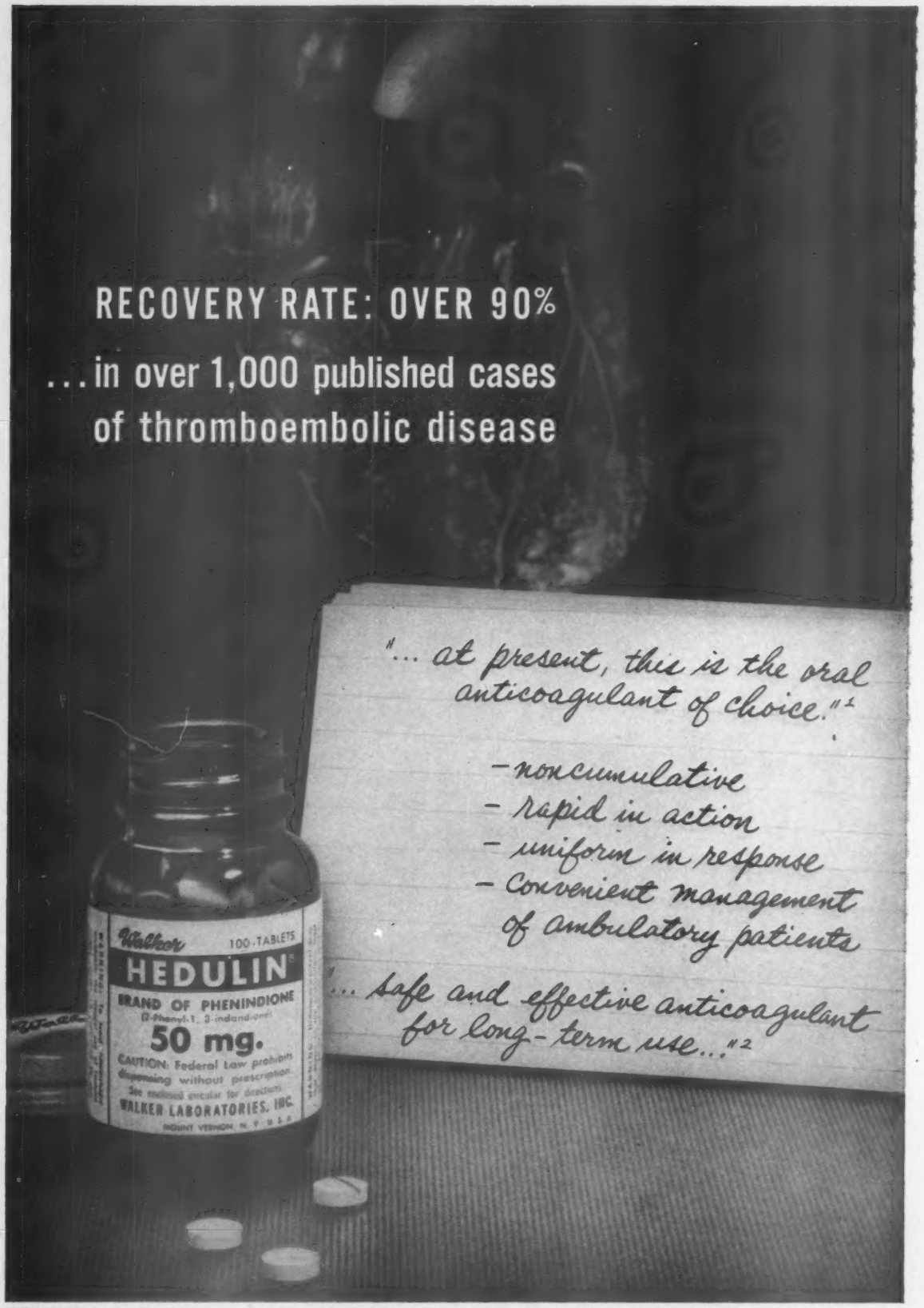

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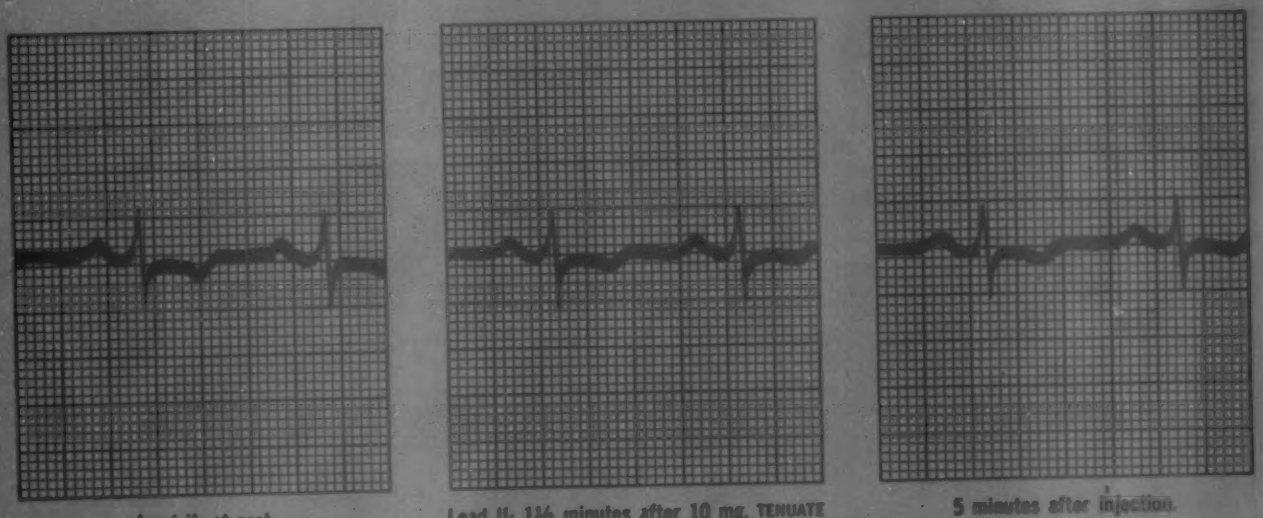

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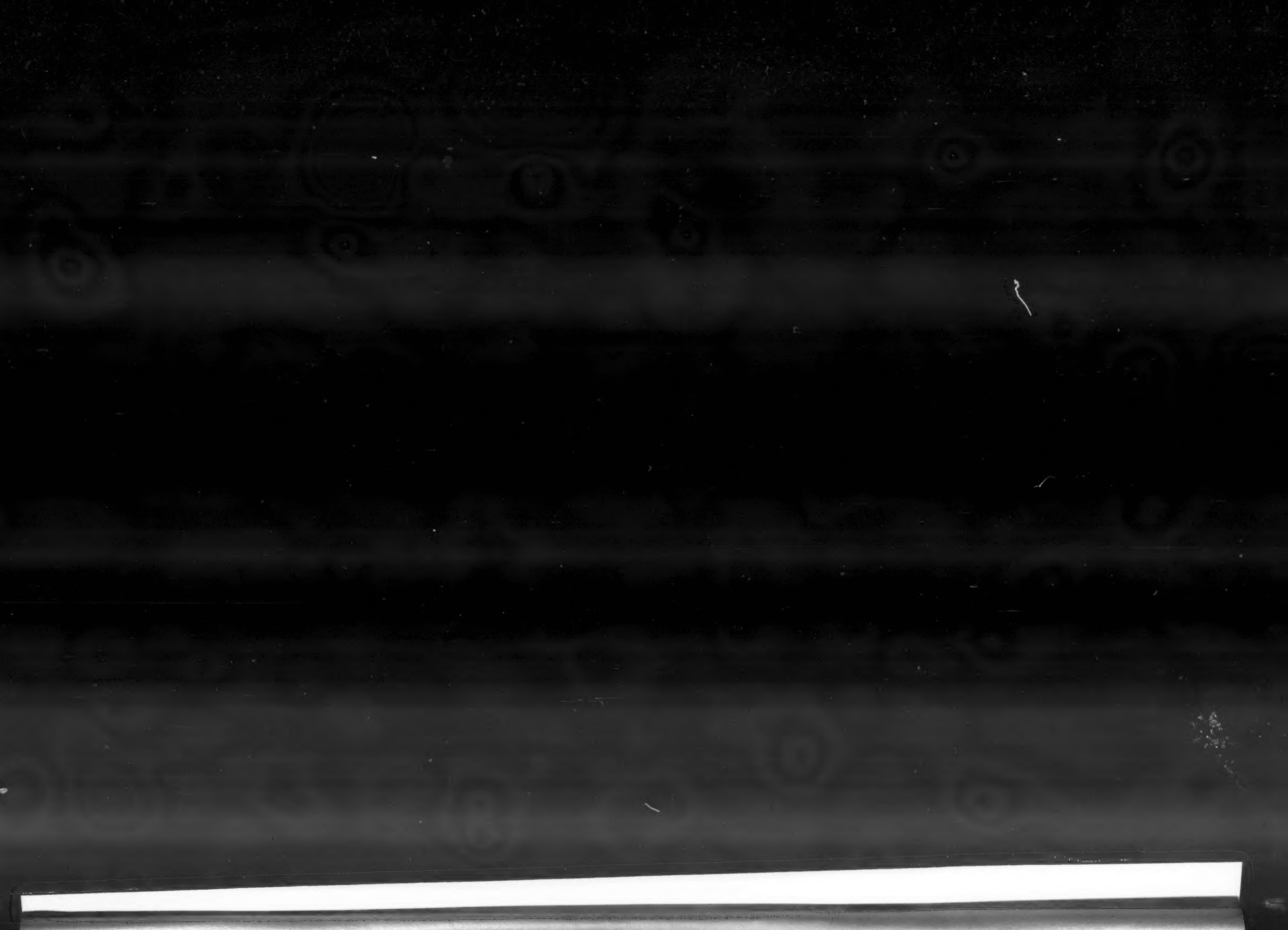

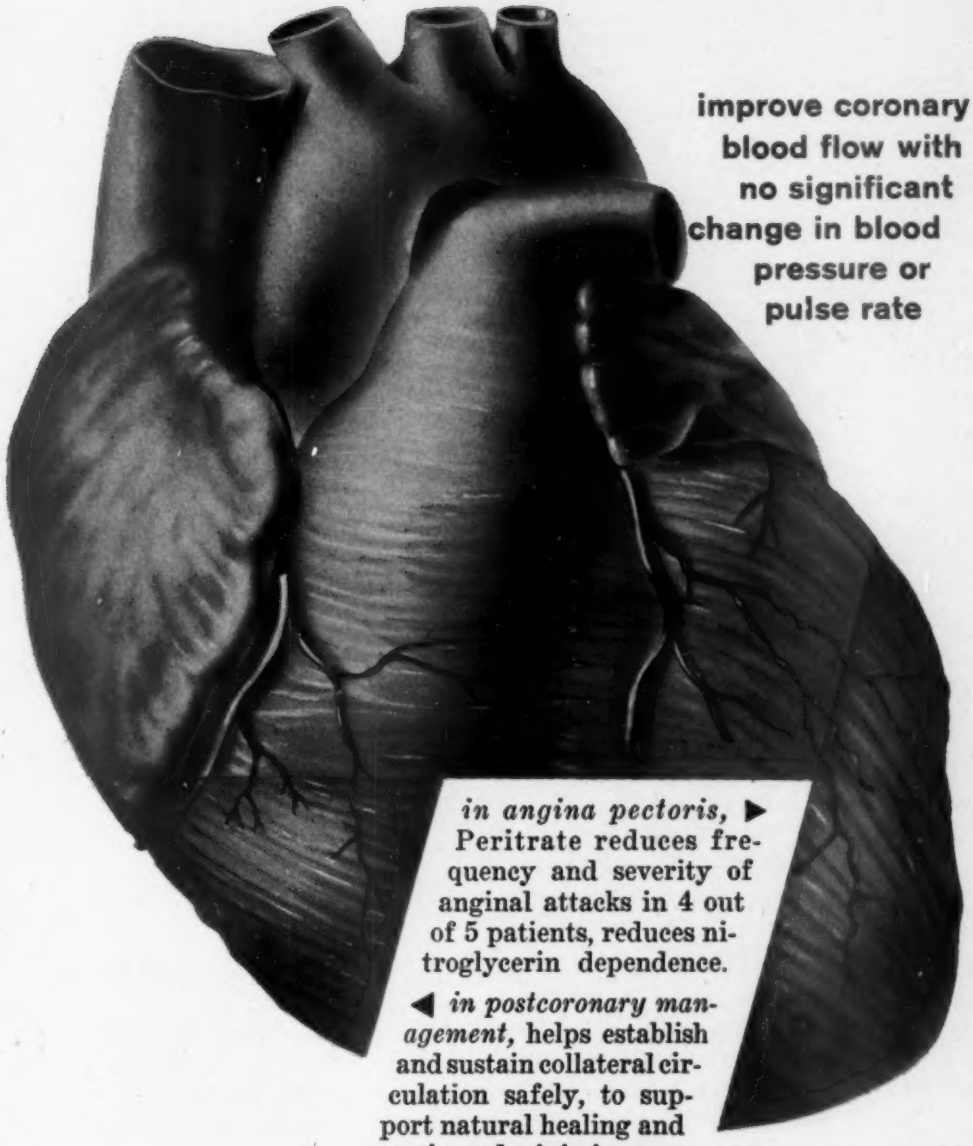

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VOLUME VI NOVEMBER 1960 NUMBER 5

EDITORIAL

Intraventricular Block

IN 1909 Eppinger and Rothberger investigated the alterations in the pattern of the electrocardiogram caused by lesions in the myocardium. Being unable to create such lesions in an acute experiment (the idea of ligating a coronary artery occurred to Smith much later), they injected solutions of silver nitrate into the ventricular wall. To their astonishment the injection of large amounts of this substance often caused only minor changes in the size of QRS complexes. Occasionally, however, a necrotic focus produced by a very small amount of silver nitrate provoked major changes and, in particular, a remarkable widening of the QRS complex. This observation led the authors to sever the main stem of the bundle branches and to the discovery of the bundle branch block pattern in the electrocardiogram.[1]

The same authors also described this abnormality in man and reported histologic findings which, to their satisfaction, proved the interruption in one of the bundle branches. This report started a fallacy which lasted many years and handicapped the development of the theoretic basis of the electrocardiogram and clinical electrocardiography. It became clear only much later, particularly through the investigations of Wilson and his school, that the bundle branch block was located on the wrong side, and what was considered right bundle branch block actually was a left one and vice versa. The "new nomenclature" was very slowly accepted and as late as 1933 Rothberger rejected it,[2] quoting a series of histologic reports by various authors supporting his original conception. This confusion and perserverance with mistaken ideas had several reasons which are of interest and have practical importance.

Topography of Conduction System: First, the histologic recognition and localization of the A-V conduction system is difficult; its topography rather than its particular structure permits identification in man. Thus the very existence and function of the A-V system have been repeatedly denied even in recent years. Several important aspects of the A-V conduction system are not clear and await elucidation. We know little about the relation between the A-V node and coronary sinus node (Zahn's node). It is established that the area at the orifice of the coronary sinus vein is endowed with a high degree of automaticity. Is this area an extension of the atrial portion of the A-V node or is it a separate unit in loose contact with the A-V node? Is it an equivalent of the sinus node? Takahashi[3] speaks of it as a lower sinus node and Doerr[4] points out that the orifice of the coronary sinus vein is situated in the former sinoatrial area and the coronary sinus node may be the equivalent of the node of Keith and Flack. Little is also known about the connections between the A-V node and the atria. In almost all textbooks on electrocardiography and physiology the A-V node is depicted as being situated in the right atrium and in contact only with its muscular bands and the right side of the atrial septum. This is certainly not correct since during A-V rhythm the left atrium of the dog contracts before the right one.[5] Connections must therefore exist between the A-V node and the left side of the septum.

Bilateral Bundle Branch Involvement: A second cause for the initial confusion in the localization of the bundle branch block in man is the finding emphasized by Mahaim[6a] and Yater,[7] namely, that in many instances both bundle branches are involved, only one more than the other. Therefore, one may assume that during the difficult and time-consuming histologic examination of the bundle branches many examiners stopped looking as soon as they found a lesion in one bundle branch. The difficulty of such investigations, on the other hand, has recently been illustrated again by the fact that the frequent

occurrence of bilateral lesions has been denied.[8]

Auxomerous Conduction: A third reason for the confusion is the experience that definite damage of the bundle branches was found histologically without the presence of a bundle branch block on the electrocardiogram. This is explained by the fact that conduction in the heart is "auxomerous,"[9] that is, it is not dependent on a certain width of the path. Cullis and Dixon[10] found that in the heart of the rabbit the smallest portion of the bundle, if undivided, "can carry all the conduction." Therefore, lesions in the common bundle and bundle branches which do not involve the whole cross section of the pathway may not impair conduction. The lower limits of this law, the smallest number of fibers necessary for conduction with normal speed, are not known.

Complete Bundle Branch Block: Arbitrarily and empirically complete bundle branch block is diagnosed by many when the width of the QRS complexes is 0.12 second or more. Mahaim[6a] described, however, an instance of bundle branch block in which the width of the QRS complex was only 0.09 second and QRS complexes of 0.11 second are not rare in right bundle branch block. On the other hand, left ventricular hypertrophy may cause QRS complexes with a width of 0.11 second, and it seems that in such cases an additional intraventricular conduction disturbance without involvement of the bundle branches may cause sufficient widening to imitate left bundle branch block. The term "complete bundle branch block" is often a misnomer because a complete interruption of conduction is not present even if the electrocardiographic pattern is typical. A delay of conduction in one bundle branch by more than 0.03 to 0.04 second causes the same picture as complete blockade since the impulse reaches the corresponding ventricle over the other bundle. In many instances of transient or intermittent bundle branch block, a delay of conduction in only one bundle existed and not "complete block."

Incomplete Bundle Branch Block: Because of the law of auxomerous conduction, incomplete bundle branch block does not seem to be caused by a lesion of only a part of the cross section of the bundle. Incomplete bundle branch block is rather a lesion in which the conduction in one branch is delayed by less than 0.04 second. With increasing delay of conduction in one bundle the QRS complexes show progressive changes since an increasing portion of the corresponding ventricle is excited via the other ventricle. Here very slight delays lead to marked changes of the QRS complexes which show features midway between the normal ones for this particular patient and bundle branch block.

Such tracings are readily obtained experimentally when one impairs conduction by exerting slight pressure on a bundle branch with the back of a knife and registers the recovery. It is striking in such experiments[11–14] how quickly, often within a few beats, recovery takes place and the QRS complexes regain their normal appearance. This is due to the fact that the pattern of the electrocardiogram remains the same in complete block (immediately after the damage of the bundle) and during the entire recovery phase until the delay at the damaged area is less than 0.04 second. We doubt, however, that this form of incomplete bundle branch block is as common in man as is often stated and that it can be as readily diagnosed as some textbooks and articles seem to assume. One reason is that the pattern interpreted as incomplete bundle branch block is often observed without any change for months and longer. It is known that a higher sympathetic tonus improves conduction in the ventricles and that improvement of even a few milliseconds would change the sequence of activation of the involved ventricle and therefore the form of the QRS complexes. However, in a study of patients with the accepted pattern of incomplete right or left bundle branch block we were not able to change the form of the QRS complexes by exercise or the inhalation of amyl nitrite, factors which alter a delayed A-V conduction markedly. Neither does carotid sinus pressure leading to a marked prolongation of ventricular diastole change such QRS complexes. Most instances of partial A-V block lessen or disappear when the electrocardiogram is taken with the patient in the erect posture and usually a very prolonged P-R interval becomes instantly normal when the patient stands. No changes in the form of the QRS complexes appear when this procedure is followed in patients with so-called incomplete bundle branch block.

Diagnosis of Incomplete Bundle Branch Block: The assuredness with which incomplete bundle branch block is diagnosed in man is in sharp contrast with the difficulty of this diagnosis. Slight widening of the QRS complex alone does not prove the existence of this lesion; on the other hand, incomplete bundle branch block even with a QRS duration of 0.13 second has been described.[15] A broader S wave in lead I

and a secondary R wave in lead V_1 can occur in normal persons and do not prove the presence of an incomplete right bundle branch block. When these waves are found in normal subjects, it is perhaps not justified to say that incomplete bundle block occurs in normal persons; it is safer to state that the activation of certain parts of the right ventricle in comparison with the left side of the ventricular septum differs from the *common* normal pattern. The differentiation of some of the described tracings of incomplete bundle branch block from patterns seen in hypertrophy of the ventricles is difficult; and until our knowledge on this question improves, it seems safer to diagnose intraventricular conduction disturbance without an attempt at further differentiation. Temporarily, for one or a few beats, an incomplete bundle branch block can appear and be diagnosed with greater certainty.[16]

Since in incomplete bundle branch block the sequence of activation of some portions of the involved ventricle differs from the normal, one must consider the possibility that similar abnormalities could appear on the electrocardiogram when branches of the main stem of the bundle branches are damaged by disease. The modifications of the electrocardiographic pattern by such lesions were investigated by two research teams[12,14] and the results were identical; they are remarkable and too often neglected. The experiments, performed on dogs, revealed that interruption of the whole anterior or posterior division of the left bundle branch soon after the bifurcation of the main bundle, or interruption of conduction in those fibers which spread toward the apex often did not change the width of the QRS complex at all. It remained 0.04 or 0.05 second despite marked changes in the form of the waves. If widening occurred in some experiments, it did not surpass 0.01 second. One must therefore conclude that activation of a major portion of the left ventricle via other pathways need not cause a widening of the QRS complexes. This result should make us cautious of a diagnosis of "incomplete bundle branch block" if QRS complexes are widened to 0.11 second or more.

The possibility has been considered, as mentioned previously, that incomplete bundle branch block originates in the main bundle branches when only a portion of the cross section is damaged. The law of auxomerous conduction would preclude this possibility unless it could be demonstrated that a functional differentiation exists in the main stem of the bundles and that certain portions of them conduct impulses to particular portions of the ventricles.

Wenckebach Phenomenon in the Bundle Branches: A conduction disturbance comparable to the Wenckebach phenomenon is another form of incomplete block. It is surprising that this form is exceedingly rare in man. When one bundle branch is completely severed in the dog heart *in situ* and pressure is exerted on the other branch with the back of the knife, complete A-V block appears at first; soon recovery takes place and during the recovery process all types of partial A-V block are readily observed.[13] Compared with this experience the rarity of partial bundle branch block in man is striking. Of course, 2:1 and 4:3 bundle branch block are observed and usually called intermittent bundle branch block. However, a gradual widening of the QRS complexes from beat to beat ending with a typical bundle branch block pattern and this in turn followed by a normal QRS complex representing a Wenckebach phenomenon in a bundle has not been described in man or in the experiment with normal rhythm and rate. One case which could be interpreted in this way has been described by Holzmann[17] but in this patient a marked ventricular arrhythmia existed. The Wenckebach phenomenon in one bundle was clearly observed in the dog[18] but only when the rate was rapid because of atrial flutter; it is known that under these conditions conduction follows special rules.

One reason for the rarity of the Wenckebach phenomenon in the bundle branch as compared with its frequency in A-V block is the fact that in A-V block after complete blocking of one beat the conduction system somehow recovers and the following impulse is conducted well. How this recovery takes place is still not understood since it is not known why the damaged tissue which just failed to conduct an impulse does it well when the next one arrives. Recovery is made more difficult in bundle branch block; because when the bundle branch does not conduct an impulse to the ventricle, the impulse arrives there via the other ventricle and is conducted retrograde in the involved bundle branch. Another reason why such electrocardiographic patterns have not been seen in man is the experience that when conduction improves after the blocked impulse in a Wenckebach phenomenon it still often remains prolonged[19] and, as pointed out previously, any delay of conduction by more than 0.04 second will cause the same pattern on

the electrocardiogram as in complete bundle branch block.

Focal and Parietal Block: Whether widening of the QRS complexes occurs because of abnormal conduction from fiber to fiber in the common myocardium (fiber block, focal block, parietal block) as opposed to a lesion of the conduction system[20] is not yet certain. Widening of the QRS complexes after injection of procaine[21] or quinidine[22] into branches of the coronary arteries need not indicate such a block since damage to peripheral branches of the conduction system cannot be ruled out. The widening of the QRS complexes seen after administration of quinidine may also involve the specialized tissue and need not indicate damage to working muscle alone. Certainly further studies of this question are required.

It seems doubtful whether widening of the QRS complexes appears as a consequence of myocardial infarction "peri-infarction" block[23] without participation of the bundle branches only because the impulse is prevented from activating the ventricular myocardium from inside out. The experiments with silver nitrate cited earlier speak against this assumption. The presence of bundle branch block and infarction would explain most of these tracings.

Arborization Block: The "arborization block," usually mentioned in quotation marks, is rare and its mechanism controversial. The very wide and very low QRS complexes are often said to be due to a lesion "below the main stem of the bundle." This seems certain but does not explain much. It is argued that the term should not be used since it implies a lesion of the Purkinje network; however, this explanation has not been seriously considered. Destruction of large areas of the subendocardial muscular layers with the smaller branches of the specialized A-V system by scraping with a small knife did not cause widening of the QRS complexes in our experience. In recent years arborization block has been attributed to focal damage of the myocardium; this is improbable in view of the experiments quoted previously. Neither could block in some ramifications of one bundle branch cause such a pattern on the electrocardiogram. We believe that complete block in one bundle branch and almost complete block in the other could cause the electrocardiographic pattern of arborization block. Thus, a complete block of the right bundle branch and a block in the left main stem below the origin of the small branch which activates the upper left septum[24] could produce this pattern; it would force the impulse to utilize mainly the common myocardium for its spread over the ventricles and the impulse would spread from a central point in all directions.[60]

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Clinical Studies

Five Year Survival of Consecutive Patients with Malignant Hypertension Treated with Antihypertensive Agents*

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THE UNIVERSALLY poor prognosis of hypertension associated with papilledema (malignant hypertension)[1–4] has been well documented. The studies of Keith, Wagener and Kernohan,[1] Schottstaedt and Sokolow,[3] and Kinkaid-Smith et al.[4] among others, have shown that 80 to 90 per cent of untreated patients with malignant hypertension die within one year and that the remaining 10 per cent rarely survive eighteen months. Early papers on the therapeutic effects of ganglionic blocking drugs and other agents designed to lower blood pressure reported that treatment increased the period of survival of patients with malignant hypertension.[2,5–12] The majority of these studies covered a follow-up period of only two or three years; only a few described the response in a series of patients treated for a substantial period such as five years. For example, Smirk,[6] in 1954, in a report on twenty-eight patients observed for three and a half years, noted that twenty-one of the treated patients survived an average of 22.8 months, in contrast to an average of one year in untreated patients. McMichael and Murphy,[9] in 1955, reported that approximately 40 per cent of thirty-two patients treated with ganglionic blocking agents survived for three year periods. Sokolow and Kaufman,[10] in a three year follow-up study on the group of cases to be reported herein, stated that of eleven patients with good renal function when first treated (creatinine clearance rates exceeding 45 ml. per minute), six survived twenty-four month, and five were still alive and active at the end of three years. Perry and Schroeder,[11] in 1956, described eighty-two patients who were treated for varying periods; of sixty-six patients who continued treatment, twenty-six were alive after an average of 21.4 months, and thirty-eight were dead after an average of 4.7 months. Dustan and co-authors[12] reported on the results of modern therapy in a series of patients seen between 1951 and 1958 and observed for periods ranging from three months to seven years. Despite the difficulty in combining data derived from such variable follow-up periods, they noted that the five year survival rate in the nineteen patients followed up for seven years was somewhat under 40 per cent.

In view of the difficulty of interpreting published data derived from incomplete and variable follow-up periods, a study was initiated to determine the effect of long term treatment with ganglionic blocking agents on patients with malignant hypertension, with special emphasis on the effect of such therapy on prognosis, the importance of initial renal function and the modifying factors and pitfalls in management.

MATERIALS AND METHODS

The subjects were twenty-six consecutive patients with malignant hypertension referred to the Hypertension Clinic for treatment during the years 1950 through 1953. Two additional patients who had

* From the Department of Medicine, University of California School of Medicine, San Francisco, California. This study was aided by grants from the United States Public Health Service (H-754), the Burroughs Wellcome & Co., Tuckahoe, New York, and the Mrs. William A. Hewitt-Deere Estate.

been included in the preliminary report published two years ago[10] did not meet the criterion for duration of therapy and were excluded from this series. The group consisted of five women and twenty-one men, averaging forty-one years of age. The average age of the women was thirty-four years or, excluding Case 2 (a nine year old girl), thirty-seven years; the average of the men was forty-two years. Twenty-three patients were white, one was Negro, one Mexican and one Japanese.

All twenty-six patients had malignant hypertension as defined by the presence of papilledema and diastolic pressures exceeding 120 mm. Hg. Patients were included for study regardless of the underlying cause of hypertension. In eight with primary renal disease, hypertension with papilledema had occurred late in the course of the disease; in fifteen with known high blood pressure for at least one year, the accelerated phase of hypertension had developed; and in three the hypertension was of recent onset. The duration of known hypertension before the onset of the malignant phase varied from fifteen years to less than one month. The duration was ten years or more in six patients and less than one year in nine patients. Two of the patients who were still alive in October 1958 had known hypertension for five and twelve years, respectively.

Eleven of the patients had adequate renal function initially as defined by a creatinine clearance rate over 45 ml. per minute, a fifteen minute phenolsulfonphthalein excretion of 25 per cent or more (after intravenous administration of 6 mg. of dye), or a nonprotein-bound nitrogen under 40 mg. per 100 ml. Renal function was impaired in the remaining group of fifteen patients, which included the eight with known primary renal disease. Considering the difficulty of detecting underlying pyelonephritis,[13-15] the actual incidence of underlying renal disease in our series may have been higher. In a previous study,[3] Schottstaedt and Sokolow stated that a pathologic diagnosis of pyelonephritis was made in 40 per cent of all cases of malignant hypertension seen at autopsy. In addition, since at that time we were not fully aware of the importance of renal artery occlusion as a cause of malignant hypertension,[16] aortograms were not done on any of the patients. This study, however, is concerned primarily with prognosis rather than etiology and will deal only with gross renal changes.

Pretreatment Studies: All patients were hospitalized for pretreatment studies and an initial period of controlled therapy. A detailed history was obtained from each at the beginning of the study and a physical examination was performed. Laboratory studies, done initially and repeated at intervals during the follow-up period, consisted of urinalysis, blood count, electrocardiogram, x-ray film of the chest, intravenous pyelogram and renal function studies, including determination of phenolsulfonphthalein excretion and creatinine clearance in most cases. Addis tests were also performed on occasion. After initial treatment, the patients were observed at follow-up clinic visits or through periodic reports from their private physicians until their death or the end of the study period in October 1958. Thus, a minimum five year follow-up was obtained on all surviving patients.

Methods and Duration of Treatment: The lack of a placebo group of patients with malignant hypertension treated similarly except for the use of ganglionic blocking agents was considered justified in view of the well documented poor prognosis in untreated patients, both by ourselves and others[1-4] (Fig. 2). The rarity of survival beyond two years or of spontaneous reversal of papilledema[13] was clearly shown in our own clinic[3] in the period immediately preceding the current study, despite intensive general care required by the severity of the illness and the progressive downhill course.

Treatment was initiated with hexamethonium chloride* administered parenterally in progressively increasing doses until a systolic blood pressure (standing) of 150 to 160 mm. Hg was obtained or until the severity of the side effects made further increases undesirable.[17] The maintenance doses used subsequently varied from 30 to 235 mg. daily. The oral route was used rarely, and only after an initial adequate response to the parenteral drug had been obtained. When pentapyrrolidinium, and later mecamylamine, became available, oral preparations of these drugs were usually employed, although two patients were maintained with parenteral hexamethonium for as long as five years. Hydralazine, up to 400 mg. daily, was added to the regimen of eighteen patients. In addition, all patients received supportive care in the form of a low sodium diet, digitalis when indicated, fluids, sedation, antibiotics for renal infection, and other measures as required.

Hypotensive therapy was begun in all cases within three months of the onset of the malignant phase. The time of onset was judged retrospectively by the appearance of severe headache, gross hematuria or visual disturbances, by our diagnosis of papilledema or by documentation of papilledema elsewhere. Treatment with ganglionic blocking drugs was continued until the death of the patient or the end of the study in all but four patients. In one of the latter, hypotensive medications were discontinued when the patient's blood pressure dropped to normal levels where it has since remained. In the other three less potent hypotensive drugs were substituted. Although controlled therapy was continued in all cases for a minimum of one month or until the malignant phase was reversed, current experience indicates that subsequent maintenance doses may have been inadequate.

Twenty-two patients died during the course of the study. Autopsies were performed on seventeen; pathologic sections were available for review in the

* Hexameton® was supplied through the courtesy of Mr. William Creasy, Burroughs Wellcome & Co., Tuckahoe, New York.

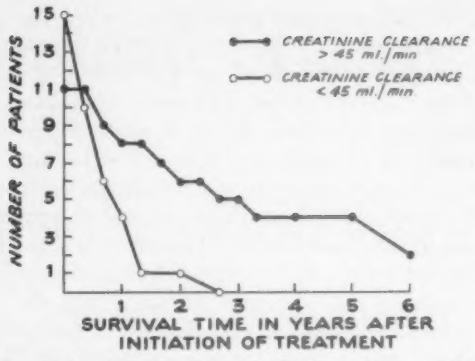

FIG. 1. Comparison of survival of patients with good and poor renal function initially, all treated with ganglionic blocking agents.

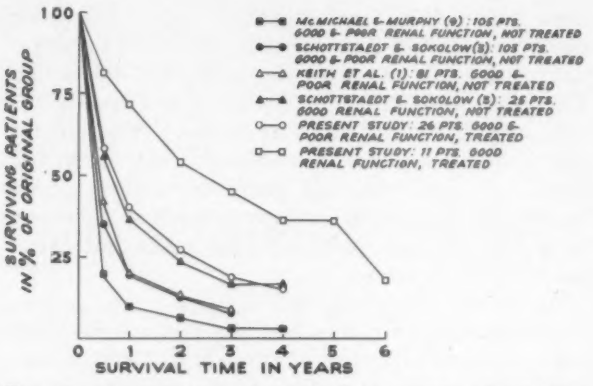

FIG. 2. Comparison of survival in groups of patients with good and poor renal function initially, treated and untreated.

ten cases examined postmortem at the University of California Medical Center.

RESULTS

Initiation of Therapy: The interval between the diagnosis of malignant hypertension and initiation of therapy was relatively short. Treatment was started during the initial development of frank papilledema in two cases, within one to two weeks in thirteen cases, within two to four weeks in six, and after more than one month in five. The average period of survival of patients in the first three groups did not differ significantly. In the group in which therapy was delayed a month or more the patients survived longer.

Symptomatic Changes: Symptomatic improvement was shown by all patients within a week of the initiation of therapy. First, the disabling headaches which afflicted more than half the patients disappeared or decreased in severity. This change was quite striking and often very sudden. Blurred vision or blindness subsided more gradually as fundal changes receded. Relief of nausea and vomiting was striking. Signs of congestive failure subsided, especially in those patients who survived early acute renal failure. Whether this can be attributed to the hypotensive medication alone is uncertain because of the concurrent use of ancillary measures.

Decrease in Blood Pressure: The diastolic blood pressure was lowered at least 20 mm. Hg in all but two patients. Persistent diastolic pressures of 100 mm. Hg or less, however, were achieved in only six patients. In the remainder, diastolic pressures were reduced from an initial level of 130—160 to 110—130 mm. Hg. These values, it must be emphasized, were derived mainly from casual readings, especially in the case of outpatients. Systolic pressures, which ranged between 190 to 240 mm. Hg before treatment, were reduced below 190 mm. Hg in all patients; only six, however, showed a consistent reduction to 150 mm. Hg or less. The variable effectiveness of therapy in lowering the blood pressure in our patients was due in part to our reluctance to reduce the pressure too drastically in patients with impaired renal function.

Papilledema: Treatment resulted in reversal of papilledema in nine of the eleven patients with good renal function and in ten of the fifteen with poor function. Eyegrounds returned to Keith-Wagener classification II or III[18] within an average of 3.3 months after the beginning of therapy. Even when reversal was not complete, the degree of papilledema decreased and some of the soft exudates and hemorrhages were resorbed. In several patients papilledema recurred just before death.

Renal Function: Renal function improved in seven patients, and proteinuria decreased or disappeared in several; an additional seven patients showed no change within the first month of therapy. In the remainder, renal function progressively deteriorated.

Electrocardiographic Changes: Serial electrocardiograms were taken on twenty patients.[19,20] They showed decrease or disappearance of the pattern of left ventricular hypertrophy or ischemia in five cases and no further deterioration in four. Progression of the electrocardiographic abnormalities occurred in the remainder, especially in those who, in retrospect, were inadequately treated.

Length of Survival: The average survival period for the entire group was twenty-one months; the patients with good initial renal

TABLE 1*

Cause of Death in Twenty-Two Treated Patients—Postmortem Findings in Sixteen

Case No.	Survival Period (mo.)	Clinical Cause of Death	Postmortem Findings					
			Heart Weight† (gm.)	Heart and Vessels	Kidney Weight (gm.)	Kidney	Lung	Brain
			Initial Renal Function: Good					
1‡	38	Uremia, CHF, terminal CVA						
2	31	Uremia, pulmonary edema	800 (2.5)	Marked aortic and coronary sclerosis	150 160	Nephrosclerosis	Atelectasis, pneumonia	Infarcts in small basal ganglia-sclerotic cere, bral vessels
3	21	Uremia, CHF, CVA	650 (2.4)	Moderate aortic and coronary sclerosis	140 160	Nephrosclerosis	Congestion, frothy	Hemorrhage of parietal cortex
4‡	19	Uremia, CHF, pneumonia						
5‡	11	Uremia						
6	5	Uremia, encephalopathy	800	Coronary sclerosis	140 180	Nephrosclerosis	Pneumonia, congestion, effusion	Normal
7‡	4	Uremia, CVA						
			Initial Renal Function: Poor					
8	28	Uremia, CHF, pneumonia	600 (2.5)	Minimal coronary sclerosis	90 90	Congenital hydroureter, hydro- and pyelonephrosis	Interstitial pneumonia, congestion	Not examined
9	15	Uremia, cerebral hemorrhage, pneumonia	450 (2.2)	Moderate coronary sclerosis	90 90	Chronic glomerulo-, pyelo- and nephrosclerosis	Congested bronchopneumonia	Infarct in internal capsule, cerebellar hemorrhage
10	15	Uremia, myocardial infarct	...	Recent and old infarcts, coronary sclerosis, dissecting aortic aneurysm	...	Chronic glomerulo nephritis		
11	12	Uremia, CHF	450 (0.8)	Minimal coronary sclerosis	90 80	Chronic glomerulo- and pyelonephritis	Congested	Not examined
12‡	9	CVA						
13	8	Uremia	760 (2.5)	Moderate sclerosis	170 170	Nephrosclerosis, necrotic arteriolitis	Pulmonary infarct, edema	Infarct in internal capsule
14	6	Uremia	750 (1.8)	Moderate coronary sclerosis	...	Nephrosclerosis, arteriolonecrosis	Congested areas of organized exudate	Not examined
15	5	Uremia, CHF	540 (1.5)	Marked aortic arteriosclerosis, minimal coronary arteriosclerosis	95 90	Chronic and subacute glomerulonephritis, nephrosclerosis, arteriolar necrosis	Congestion	Normal
16	5	Myocardial infarct	746 (1.7)	Coronary sclerosis, thrombosis, infarct	180 170	Nephrosclerosis, arteriolar necrosis	Congestion	Edema, extensive cerebral arteriosclerosis
17	4	Uremia, pneumonia	370 (1.2)	Moderate coronary sclerosis	50 50	Nephrosclerosis	Extensive bilateral interstitial pneumonia	Ischemic changes in basal ganglia
18	3	Uremia, CHF	510 (2.1)	Moderate coronary sclerosis	80 70	Chronic pyelonephritis, nephrosclerosis	Chronic passive congestion, acute pulmonary edema	Cerebellar edema
19	2	Uremia, CHF, encephalopathy	590 (2.5)	Minimal sclerosis	240 245	Nephrosclerosis, arteriolar necrosis	Congestion	Edema
20	2	Uremia, CVA	510 (2.0)	Coronary and aortic sclerosis	150 150	Nephrosclerosis	Normal	Old hemorrhage, sclerosis of vessels
21‡	2	Uremia, pulmonary edema						
22	1	Uremia, CHF	280 (child)	Normal coronaries and aorta	45 45	Chronic pyelonephritis	Effusion, congestion, areas of fibrosis	Edema

* Four of the twenty-six patients were still alive at the end of the study period.
† Figures in parentheses = thickness of left ventricular wall in centimeters.
‡ No autopsy performed.
CHF = congestive heart failure.
CVA = cerebrovascular accident.

function survived an average of thirty-nine months and those with poor initial renal function an average of 7.8 months. Data on the survival of the patients in the two groups are compared in Figure 1. Similar data reported by various investigators[1,3,9] are compared in Figure 2. Of the eleven patients with good initial renal function, three died in the first year, two in the second, one in the third and one in the fourth year. The remaining four were still alive in October 1958, five to six years after the beginning of therapy. Two of the four died subsequently, one of acute myocardial infarction and ventricular fibrillation and one during anesthesia for a gynecologic procedure; the other two were still alive in the seventh year of follow-up. Despite therapy none of the fifteen patients with impaired renal function survived longer than twenty-eight months. Twelve died within the first year (eight within the first six months). The remaining three patients, two of whom had primary renal disease, died fifteen, fifteen and twenty-eight months, respectively, after the beginning of treatment. The cause of death and postmortem findings are listed in Table I.

Comments

Our results confirm published observations[4,6,12,21,22] that treatment with ganglionic blocking agents will lengthen the survival of patients with malignant hypertension, and in some cases completely reverse the malignant process. The importance of initial renal function as a prognostic factor, as noted by Sokolow and Schottstaedt[3,23] in 1953, is also re-emphasized in this study.

Treatment with hexamethonium did not significantly prolong the life span of patients in terminal renal failure with uremia over that of untreated patients. In patients with primary renal disease or nephrosclerosis with moderate renal impairment, treatment resulted in temporary arrest of the downhill course, allowing the patient's return to useful activity for a time, even though the underlying renal process was not reversed. In patients with good renal function, adequate therapy usually reversed the process completely or at least arrested it, thereby lengthening the period of survival. The fact that the greatest number of deaths in this series occurred within the first six months of therapy, however, indicates that treatment should be instituted promptly before renal function deteriorates.

The major unpredictable factor in survival is the extent of atherosclerosis of the coronary and cerebral vessels before treatment, since thrombosis or hemorrhage of these vessels may cause death, even when the blood pressure is under control and there is no further renal deterioration. Also, in the accelerated phase of hypertension, atherosclerosis may be irreversible and may even progress even though the pressure is controlled.

In the early 1950's it was feared that substantial lowering of the blood pressure might lead to myocardial or cerebral infarction or acute renal shutdown. Subsequent experience has shown that gradual lowering of the pressure is well tolerated, even in cases of advanced vascular disease.[22,24] Decreasing the blood pressure may also result in reversal of the pathologic changes of the malignant phase, as shown by the work of Masson and associates[25] in rats and McCormack et al.[26] in man.

The degree of improvement in our patients, and perhaps the length of survival, might have been increased by use of more vigorous and better controlled therapy, as advocated by Perry and Schroeder.[11] The lengthened period of survival in their series of eighty-two patients with hypertension and azotemia was due probably primarily to the vigor with which therapy was pursued.

Summary and Conclusions

Twenty-six patients with malignant hypertension were treated with ganglionic blocking agents and followed up for a period of at least five years, or until death. Of eleven patients with satisfactory renal function initially (creatinine clearance greater than 45 ml. per minute), four patients survived five years or longer. Of fifteen patients with poor renal function initially, none survived three years. In the patients with good renal function when first seen, death was due to atherosclerotic complications, not to cardiac or renal failure.

The accelerated phase of hypertension can be reversed if intensive therapy is instituted before severe renal failure has developed. Approximately 40 per cent of patients treated before renal function is less than half normal can be expected to survive five years. With more meticulous control of therapy, the rate of survival probably can be improved. The unpredictable development of atherosclerotic complications is the critical factor in determining length of survival. It is to be emphasized that the

addition to hypotensive therapy of measures for treating atherosclerosis, as they become available, may prolong survival even further.

Impaired renal function alters the prognosis and if severe, may preclude the use of hypotensive drugs. Impaired renal function *per se*, however, is no reason for withholding therapy. Cautious lowering of the blood pressure, with serial observations of renal function, may improve renal function or prevent its further deterioration. Slightly impaired renal function in association with severe hypertension is an indication, not a contraindication, to the use of drugs to lower the blood pressure.

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Cardiac Insufficiency in Chronic Alcoholism*

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THE RELATIONSHIP between malnutrition and heart disease has long been recognized. At one time thiamin deficiency, beriberi, was thought to represent the only cause of this type of cardiac insult. However, in recent years there has been a growing appreciation of the occurrence of heart disease as a result of multiple nutritional deficiencies. Recently attention has been directed to the possible role of chronic alcoholism in the genesis of cardiac disease, probably because alcoholism causes malnutrition rather than because of any evidence of the cardiotoxicity of alcohol *per se*. Such problems of heart disease due to dietary deficiencies remain unsolved, and considerable difficulty exists regarding the diagnostic features of various types of nutritional heart disease. Nutritional cardiac disturbances may be associated with other cardiac problems. For example, the cardiac complications of thyrotoxicosis and pregnancy may be due in part to dietary inadequacies. With the appreciation of these facts and with the recognition that malnutrition is one of the most common disease states from which man suffers, the significance of nutritional heart disease becomes apparent.

For some time we have been aware of different clinical syndromes of heart failure associated with alcoholism. Many patients with chronic alcoholism have not exhibited the classic clinical features and course of beriberi heart disease. In view of the state of knowledge concerning nutritional heart disease, it seemed worth while to publish these observations.

CASE REPORTS

CASE 1. R. C., a forty-five year old white man, was first hospitalized in December 1956 because of edema and dyspnea of one week's duration. He had similar symptoms approximately one month prior to admission in association with bilateral exertional calf pain and questionable tenderness. This latter episode disappeared spontaneously. During the week preceding hospitalization he had noted transitory periorbital edema. The patient had been a chronic alcoholic, drinking heavily for many years and had followed a grossly deficient diet.

Physical examination revealed a poorly nourished male in moderate respiratory distress. Blood pressure was 126/60 mm. Hg, and pulse rate was 96. In addition to basilar rales, there was cardiac enlargement and a diastolic gallop rhythm. The liver extended 3 cm. below the right costal margin. The electrocardiogram was compatible with early right ventricular hypertrophy (Fig. 1). Teleoroentgenogram revealed cardiomegaly with some prominence of the pulmonary outflow tract (Fig. 2). Liver function tests were consistent with the clinical diagnosis of Laennec's cirrhosis. In addition to hypochromic microcytic anemia and a blood urea nitrogen level of 38 mg. per cent, the only other aberration noted in extensive laboratory testing was hyponatremia ranging from 120 to 125 mEq./L. During the first week of hospitalization the patient was digitalized and placed on a maintenance dose. Salt restriction was imposed and a nutritious diet with supplemental multiple vitamins was provided.

Clinical Course: The patient continued to manifest increasing degrees of edema, weight gain and dyspnea. Roentgenography indicated further cardiac enlargement. After seven days of obvious deterioration, the patient's condition stabilized. Mercurial diuretics and supplemental oral thiamin chloride were begun and continued. Subsequently the patient exhibited gradual improvement. Digitalis was discontinued at the end of the third week of hospitalization. By this time the blood urea nitrogen and serum sodium concentration had returned to normal and the patient had lost 15 pounds. After a total of six weeks of hospitalization, the heart had returned to normal size (Fig. 2) and the patient was discharged.

Second Admission: Approximately one year later he was rehospitalized because of difficulty in walking. Paresthesias and weakness of both lower extremities had appeared two months prior to admission and progressed in severity until the patient could not walk. He had continued to drink heavily and to

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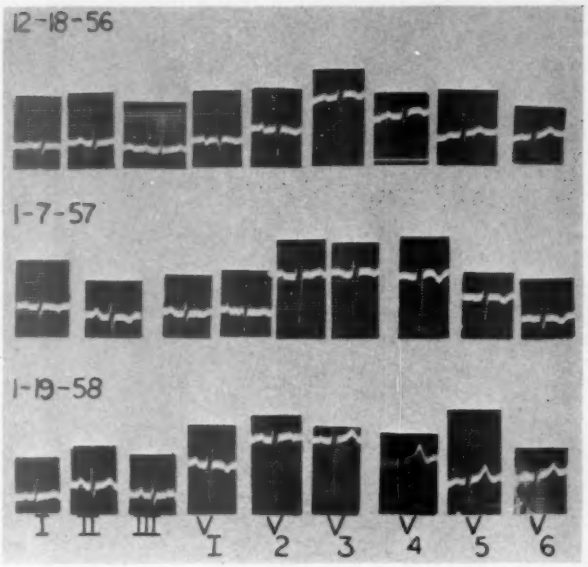


FIG. 1. Case 1. Serial electrocardiograms. Changes compatible with early right ventricular hypertrophy were present initially but promptly disappeared with treatment.

follow a deficient diet since his discharge from the hospital one year previously. Examination revealed the blood pressure to be 140/80 mm. Hg and the pulse rate 96. The only abnormal physical findings were loss of the Achilles and patellar deep tendon reflexes bilaterally. Liver function tests were once more consistent with cirrhosis. Teleoroentgenogram revealed slight cardiomegaly, minimal pneumonitis and a limited pneumothorax (Fig. 2C). The electrocardiogram was within normal limits (Fig. 1.) The pulmonary infiltrate and pneumothorax disappeared without specific therapy. In addition to a nutritious diet and multivitamin therapy, supplemental thiamin chloride was given. Because of persistent tachycardia, exertional dyspnea and demonstrable cardiomegaly, the patient was digitalized without appreciable benefit. He was discharged ambulant after eight weeks of hospitalization to continue outpatient supervision.

Comment: Although peripheral neuropathy did not appear until one year after congestive heart failure occurred, it appeared that this patient had beriberi heart disease, chronic general malnutrition and alcoholism. No response to digitalis and salt restriction was noted. Although improvement began after diuretic therapy was started, it also occurred after an interval usually expected with intensive oral treatment of beriberi. The persistence of cardiac disease in spite of treatment, noted during the second hospitalization, is consistent with the history of continued malnutrition and with the development of permanent heart disease. This has been reported frequently in beriberi.

When hepatic cirrhosis is associated with chronic alcoholism, clinicians debate the role of alcohol in the production of liver disease. The situation is very similar in the cardiac status of this and the patients to be described. To ignore the role of alcohol in the production of cardiac disease is to ignore a factor which is known to damage cells and alter their function. It would appear quite possible that alcohol was an important contributing etiologic factor. That alcohol was imbibed in large quantities is fully established in this patient, and its possible role in the production of myocardial damage must be considered.

CASE 2. L. B., a thirty-two year old white bartender, was hospitalized in July 1955 because of exertional dyspnea and calf pain. He had been asymptomatic until three weeks prior to admission, when exertional dyspnea, cough with blood-tinged sputum, and bilateral calf tenderness and pain on exertion developed. His past history was noncontributory with the exception of a long history of excessive alcohol ingestion and dietary inadequacy.

On examination, his blood pressure was 134/88 mm. Hg, pulse 120 and respiration 22. There was edema in the lung bases. In addition to moderate cardiomegaly, a diastolic gallop rhythm was noted. The liver was palpated 2 cm. below the right costal margin. There was no calf tenderness but the deep tendon reflexes were depressed in the lower extremities. Venous pressure was 160 mm. of water and the arm to tongue circulation time twenty seconds. Laboratory studies revealed slight decrease in serum albumin/globulin ratio and bromsulfalein retention of 25 per cent. Teleoroentgenograms revealed moderate generalized cardiomegaly, particularly of the left ventricle, with associated pulmonary congestion. The electrocardiogram was normal except for inverted T waves in lead I.

The patient was treated with salt restriction, supplemental vitamins, a nutritious diet and bedrest. Within six weeks he was asymptomatic, his electrocardiogram and heart size having returned to normal.

Comment: This patient's history, extrathoracic physical findings, electrocardiograms and remarkable response to good nutrition are all in keeping with heart disease due to nutritional deficiency. The features of cardiac insufficiency presented on admission were in no way different from those found in the more common types of heart failure. Again, this patient consumed large quantities of alcohol, and alcoholic intake was stopped during therapy. This was associated with recovery.

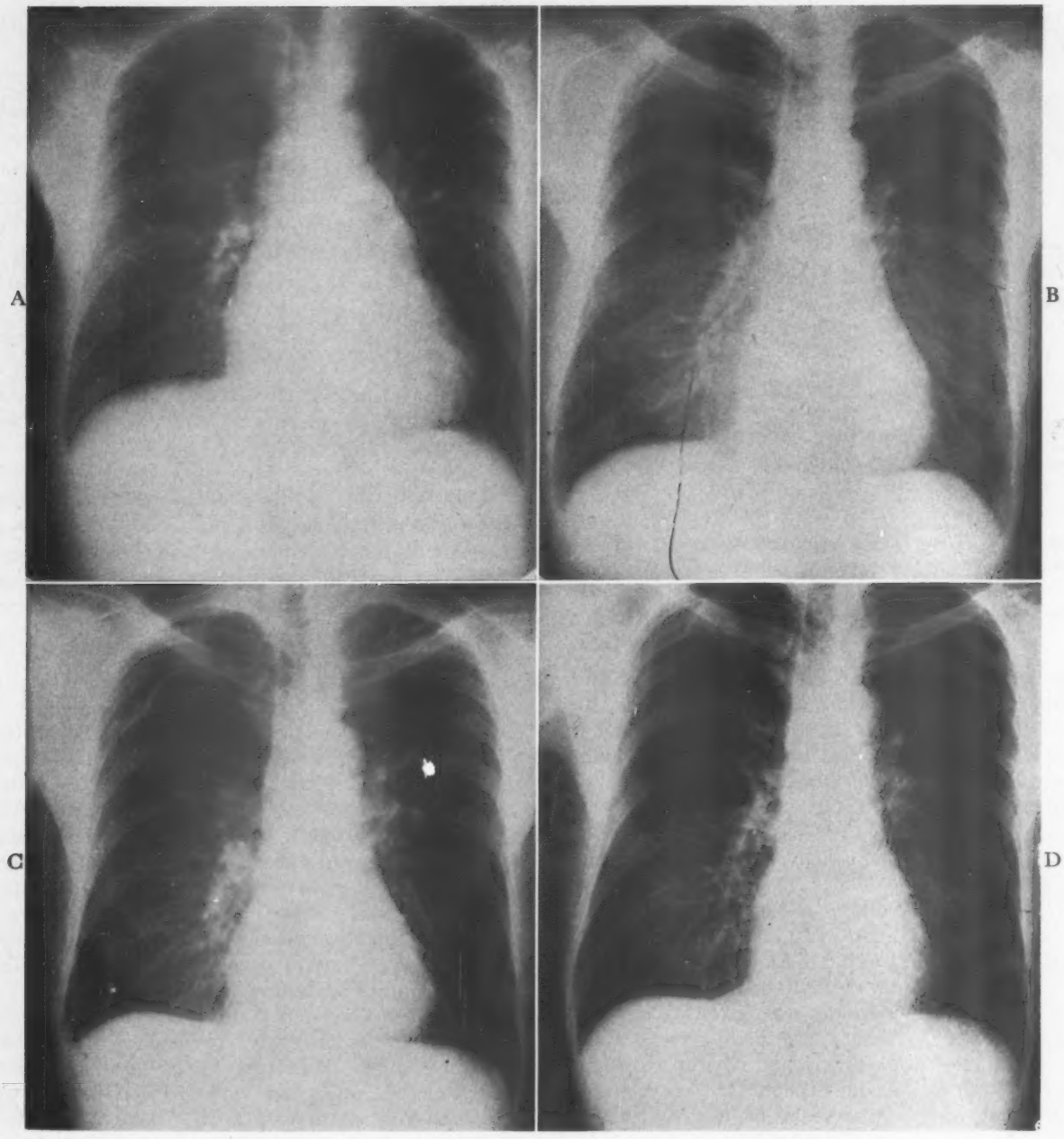


FIG. 2. Case 1. Serial teleoroentgenograms. A, taken on admission to hospital on December 13, 1956; B, taken on December 31, 1956; C, taken on January 8, 1958; D, taken on February 8, 1958.

CASE 3. F. E., a thirty-seven year old Negro man, was hospitalized in May 1958 because of dyspnea and abdominal swelling of one month's duration. Although previously in good health, he noted the gradual onset of dyspnea, abdominal swelling, pedal edema and cough. Past history was negative with the exception of ten years of chronic alcoholism and of malnutrition beginning some months preceding the onset of the present illness.

Examination revealed a blood pressure of 110/75 mm. Hg and a pulse rate of 120. There was marked cardiomegaly, a loud blowing apical systolic murmur and a diastolic gallop rhythm. There was edema in both lung bases, moderate ascites, pedal edema and enlargement of the liver to 4 cm. below the right costal margin. The arm to tongue circulation time was thirty-eight seconds. Laboratory studies were within normal limits. Teleoroentgenograms of the chest revealed pulmonary congestion, minimal pleural effusion and generalized cardiomegaly. Electrocardiograms indicated generally low voltage of T waves with inversion in all precordial leads.

Treatment consisted of digitalis, diuretics, salt restriction, supplemental multivitamins and a nutritious diet. On this regimen the patient became asymptomatic, free from edema and showed a

reduction in heart size to normal in less than two weeks. Digitalis was discontinued and he was discharged to duty after one month's hospitalization.

Comment: This patient presented the picture of severe congestive heart failure of the usual type. His rapid, complete recovery and history of dietary inadequacies are the only features to suggest a nutritional basis for the cardiac disease, except for the absence of any other detectable etiologic process. This patient also had consumed large quantities of alcohol. This was discontinued during therapy.

CASE 4. S. K., a forty-eight year old white man, was hospitalized in December 1956 because of exertional dyspnea. Four months prior to admission the patient experienced a rather severe upper respiratory infection which gradually subsided without treatment. However, pedal edema and exertional dyspnea which had appeared during the course of the infection became progressively more severe. Shortly before admission to the hospital, abdominal swelling was noted for the first time. Past history and system review were noncontributory with the exception of a long history of excessive alcohol ingestion.

Physical examination revealed cervical venous distention, marked cardiomegaly, bilateral pulmonary congestion, a diastolic gallop rhythm and hepatomegaly. The blood pressure was 120/90 mm. Hg and the pulse rate 106. Teleoroentgenograms indicated generalized cardiomegaly. The electrocardiogram revealed broadening of P waves in the standard leads, inversion of T waves in lead I and in all precordial leads, and isoelectric T waves in leads II and III. All other laboratory studies were within normal limits.

Clinical Course: The patient was treated with digitalis, salt restriction, supplemental vitamins and a nutritious diet. Diuresis resulted in an 18 pound weight loss within seven days. All symptoms of congestive heart failure disappeared. There was little reduction in cardiac size, however. The inverted T waves remained in the standard leads and V_4 to V_6 The patient was discharged to outpatient status after two weeks of hospitalization. Follow-up examination four months later revealed further reduction in heart size although the heart was still large. The patient continued on digitalis and complained little of orthopnea and exertional dyspnea.

Comment: None of the usual causes of heart disease could be found in this patient. Chronic alcoholism and malnutrition were present and could have produced the heart disease. The appearance of symptoms of heart failure during the latter part of a severe respiratory infection are consistent with the precipitation of beriberi by the increased thiamin requirements of the infectious state. However, the possibility of myocardial damage due to infection cannot be dismissed. The clinical picture was not typical of beriberi heart disease. Prompt response to therapy, even though only to a limited extent, favors a nutritional disturbance. The entire clinical course was typical of that seen in alcoholism. Although malnutrition may have been an important factor in the production of the disease and the myocardial damage, irreversible toxic effects from the alcohol cannot be ignored as a possible important contributing etiologic factor.

CASE 5. A. A., a thirty-six year old Negro man, was admitted to the hospital in May 1958 complaining of dyspnea of two weeks' duration. This symptom appeared acutely and was soon followed by progressive abdominal swelling and paroxysmal nocturnal dyspnea. He had been a severe chronic alcoholic for at least fifteen years and had been treated on several occasions for delirium tremens. With the onset of symptoms he discontinued alcohol and "began to try to eat" after many months of little food intake.

Physical examination revealed cardiomegaly, accentuation of the second pulmonic sound and a blowing systolic murmur in the second left interspace. The blood pressure was 110/45 mm. Hg and the pulse rate 100. The liver was palpated 3 cm. below the right costal margin and ascites was present. The arm to tongue circulation time was thirteen seconds and the venous pressure 265 cm. of water. Laboratory studies were within normal limits with exception of bromsulfalein retention of 24 per cent and reduction in the albumin/globulin ratio. The initial electrocardiogram (Fig. 3) showed low T waves in leads I and II, and inversion of T wave in leads V_4 to V_6. There was a prominent slurred S wave in leads I and V_1. These manifestations indicated early right ventricular hypertrophy. Teleoroentgenography revealed generalized cardiomegaly with bilateral pulmonary congestion (Fig. 4A).

Course: The patient was treated with salt restriction, a nutritious diet with supplemental vitamins, and 1 gm. of chlorothiazide daily for ten days. During the first seventy-two hours of hospitalization he gained 5 pounds and experienced some worsening of symptoms. In the succeeding seven days he lost 30 pounds, became asymptomatic, and his electrocardiogram returned to normal (Fig. 3). There was a significant decrease in heart size (Fig. 4B). After one month he was discharged from the hospital. Two months after having been admitted to the hospital he was allowed to return to work. At that time cardiomegaly was much less marked but persisted.

Comment: Initially this patient did not respond to salt restriction, diuretics and bedrest

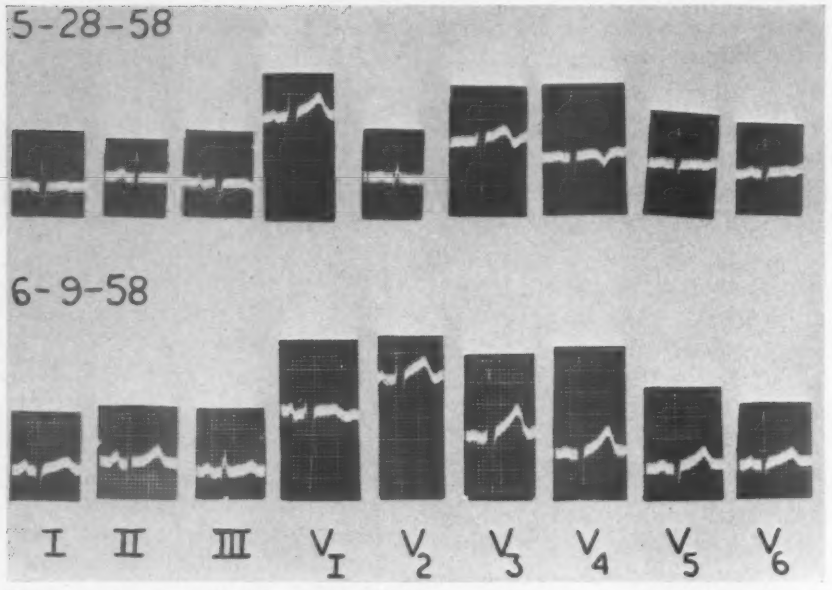
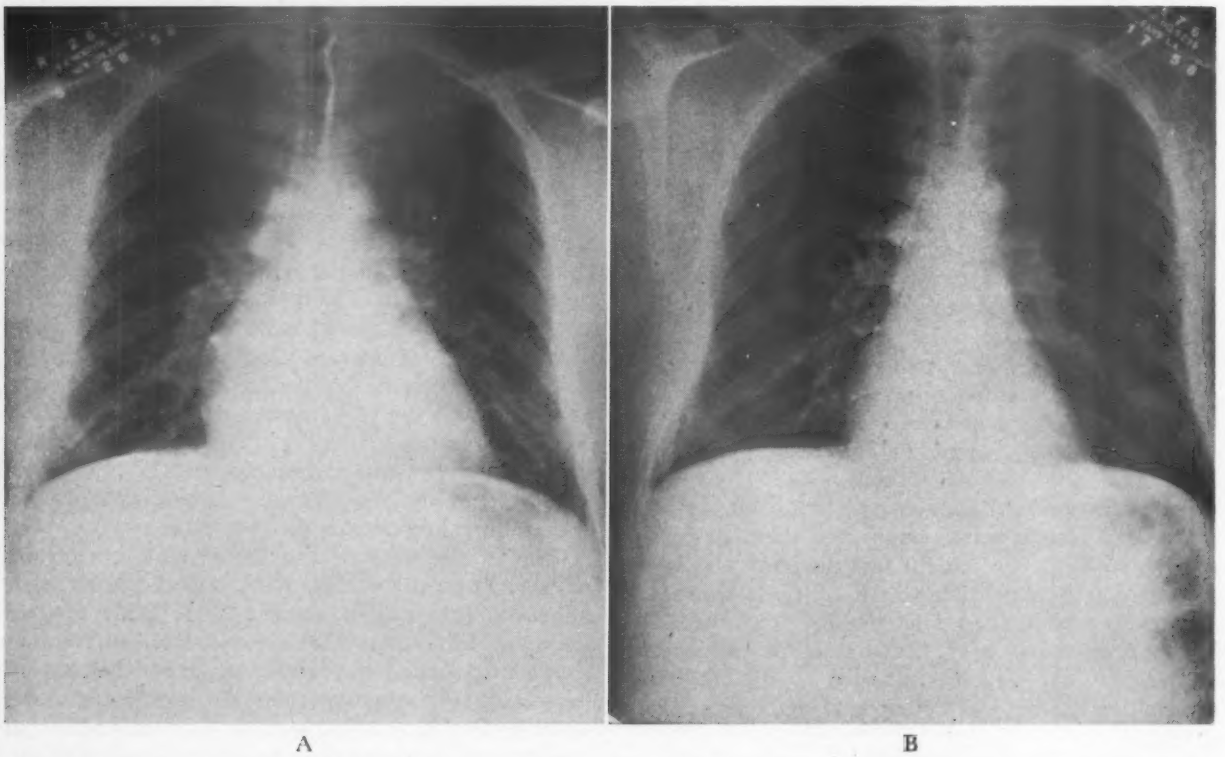


FIG. 3. Case 5. Serial electrocardiograms taken at time of admission to hospital and after approximately ten days of treatment. The initial findings, consistent with early right ventricular hypertrophy, are not present on the second tracing.



A B

FIG. 4. Case 5. A, x-ray film of chest taken on admission to hospital on May 28, 1958; B, x-ray film of chest taken on June 17, 1958. Cardiac enlargement noted initially is no longer present.

but became worse during the first three days of treatment. During this same period he was treated with oral vitamins and a nutritious diet; alcoholic intake was stopped. After the initial lag he responded rapidly and dramatically, as would a patient with nutritional heart disease. His initially rapid arm to tongue circulation time is consistent with the diagnosis of beriberi heart disease, as is the widened pulse pressure and predominently right-sided heart failure.

He returned to full duty too early, however. The clinical picture and possible etiologic factors for the myocardiopathy are similar to those in the previous patients.

CASE 6. L. B., a thirty-five year old barber, was hospitalized in January 1958 because of possible pulmonary infarction. Two weeks prior to admission he experienced the sudden onset of cough, chest pain and dyspnea. These symptoms became more severe during the succeeding twelve days, resulting in admission to another hospital. The diagnosis of auricular fibrillation, congestive heart failure and possible pulmonary embolism was made, and the patient was digitalized. After forty-eight hours he was transferred to the Charity Hospital, suffering from delirium tremens. Past history was not significant except for severe chronic alcoholism and a poor diet.

Physical examination at the time of admission revealed the temperature to be 103°F., blood pressure 102/64 mm. Hg and pulse 110. Moderate dehydration and delirium tremens were present. There was considerable cardiomegaly with a diastolic gallop rhythm. The electrocardiogram revealed inversion of the T waves in leads I, V_5 and V_6. Teleoroentgenography confirmed the presence of considerable cardiomegaly, but no pulmonary lesions were seen. All laboratory studies were within normal limits with the exception of a mild leukocytosis. The patient had a mild pneumonitis which was treated with parenteral antibiotics. Within five days the patient became afebrile and asymptomatic. He promptly deserted the hospital.

Subsequent Course: Three months later he was rehospitalized at the request of his private physican. The patient stated that following his first hospitalization he returned to work and continued drinking heavily. He felt weak and easily fatigued. About one month after deserting the hospital, he noted the onset of exertional dyspnea and occasional sporadic syncopal episodes. These symptoms persisted until the time of admission. Four days prior to rehospitalization paroxysmal nocturnal dyspnea developed with pink frothy sputum and severe orthopnea. His family physician began digitalization and referred him to the hospital.

Physical examination on admission revealed a pulse rate of 112 and a blood pressure of 120/70 mm. Hg. In addition to cardiomegaly and a soft blowing apical systolic murmur, there was a diastolic gallop rhythm. Generalized cardiomegaly was present on the admission teleoroentgenogram of the chest. The electrocardiogram revealed inversion of T waves in leads I, II, aVL, and V_4 to V_6, with isoelectric T waves in V_2 and V_3. The remainder of the laboratory studies were within normal limits.

The patient received digitalis, a nutritious diet and supplemental vitamins. He rapidly improved and was discharged asymptomatic to duty in six weeks. Teleoroentgenograms revealed that the heart had returned to normal size within six weeks after admission to the hospital.

Comment: During the initial hospitalization this patient presented evidence of heart disease and chronic alcoholism. Once more the appearance of an infectious process may have precipitated the clinical manifestations. However, the patient left the hospital before evaluation could be completed. With continued drinking and poor nutrition, symptoms of cardiac insufficiency became apparent and progressed in severity until he was readmitted to the hospital. His left ventricular failure responded completely to routine treatment.

CASE 7. E. E., a thirty-six year old Negro man, was hospitalized in April 1959 with a complaint of shortness of breath. Two weeks prior to admission he noted the onset of progressive exertional dyspnea and pedal edema. In the week preceding hospitalization he experienced repeated episodes of paroxysmal nocturnal dyspnea. Past history was not remarkable with the exception of a five to six-month history of the ingestion of at least 1 quart of port wine daily. Prior to this time his consumption of alcohol had been heavy, but his diet appeared adequate. However, during the period of increased consumption of alcohol his diet had become grossly inadequate.

Physical examination revealed the blood pressure to be 128/110 mm. Hg and the pulse 96. Bilateral pulmonary congestion was present. In addition to gross cardiomegaly a diastolic gallop rhythm was noted. There was marked pitting edema to the level of the sacrum. Laboratory studies were within normal limits with the exception of moderate eosinophilia and elevation of the sedimentation rate. Teleoroentgenograms indicated generalized cardiomegaly, bilateral pulmonary congestion and a right pleural effusion. Initial electrocardiograms revealed inversion of T waves in leads I, aVL and V_6.

Treatment consisted of salt restriction, digitalization, diuretics, a nutritious diet and elimination of alcoholic intake. Within one week the patient lost 20 pounds and exhibited dramatic symptomatic improvement. After an additional ten days his heart had returned to normal size and he was completely symptom-free. After a total of four weeks' hospitalization he returned to work.

Comment: Once more the clinical picture was typical, severe combined ventricular failure. With the exception of his dietary history this patient had nothing to suggest berberi. His complete response to routine treatment was dramatic. There was no clinical evidence of malnutrition except for the history. However, as in the other patients of this study, he had a

heavy intake of alcohol. The latter was discontinued in association with the other measures and recovery ensued. The possible etiologic role of alcohol in the production of the cardiac damage in this patient is more evident than in the patients described previously.

CASE 8. N. W., a thirty-six year old Negro man, was hospitalized with a chief complaint of swelling of the feet and abdomen. During the six months preceding admission he had noted pedal edema. During the week immediately preceding hospitalization abdominal swelling, exertional dyspnea and finally episodes of paroxysmal nocturnal dyspnea developed. He had been drinking at least one-fifth of a gallon of whiskey daily during the five years preceding hospitalization. However, his diet had been adequate until the last year.

Physical examination revealed cardiomegaly, a blowing apical systolic murmur and ascites. Venous pressure was 250 mm. of water; arm to tongue circulation time was twenty seconds. Laboratory studies revealed 24 per cent retention of bromsulfalein and an albumin/globulin ratio of 1/1. Teleoroentgenograms revealed generalized cardiomegaly. Serial electrocardiograms indicated left ventricular hypertrophy and changes suggestive of right ventricular hypertrophy. Liver biopsy showed portal fibrosis with fatty metamorphosis and focal hepatocellular necrosis.

The patient was treated with bedrest, supplemental thiamin hydrochloride and elimination of alcohol intake. Within one week he lost 26 pounds and became asymptomatic. His heart returned to normal size within four weeks of admission to the hospital, and liver function tests were within normal limits on discharge.

Comment: The history of malnutrition, a rapid arm to tongue circulation time, right ventricular failure, and the complete and dramatic response to thiamin therapy are all factors which favor the diagnosis of beriberi heart disease. Persistence of the left ventricular hypertrophy pattern on the electrocardiograms suggested the possibility of permanent cardiac damage although these findings may disappear in time. However, as in the other patients, alcohol played a prominent role in the patient's illness. Toxic damage to the myocardium certainly is possible.

COMMENTS

Since Aalsmeer and Wenckebach[1] published the first complete descriptions of beriberi heart disease, diagnostic boundaries have been repeatedly extended until there are no longer any generally accepted criteria of thiamin-deficient heart disease.[2–10] The initial impression of predominant right heart failure with hyperkinetic circulation was superseded by the syndrome of nonspecific heart failure accompanied by peripheral neuropathy or pellagra. In turn, the last version was followed by that of any undetermined type of heart failure which occurs in the presence of a deficient diet and responds to thiamin. Not all cases of beriberi heart disease respond promptly to thiamin and some severe, chronic instances of this type of heart disease fail to respond significantly. Thus the current concept represents in fact a further extension of diagnostic criteria.

VITAMIN DEFICIENCIES AND HEART DISEASE

The relationship of vitamin deficiencies other than thiamin to cardiac disease is even more tenuous. In the case of niacin, the issue is clouded by the frequent coexistence of thiamin and other vitamin (known and unknown) deficiencies. Several reports[11–13] have indicated the presence of electrocardiographic abnormalities in pellagrous patients. One report noted that such abnormalities failed to respond to thiamin but disappeared with niacin therapy.[14] There are no clinical or necropsy evidences of myocardial involvement in man with pellagra.

Although pyridoxine deficiency has never been correlated with cardiac disease in man, there is ample evidence of its effects on the cardiovascular system of animals. Thus in dogs[15,16] cardiac insufficiency and death occurred with pyridoxine deprivation. Autopsy studies revealed enlargement of the right-sided chambers of the heart and chronic passive congestion of the liver. Hypertension was noted in this species, as in rats rendered deficient in pyridoxine. In the latter instance, however, there were no lesions attributable to the deficiency state.[17]

Scurvy has been reported to produce cardiac enlargement, primarily of the right chambers.[18] However, such cases are rare. Often the diagnoses have been questioned, either with respect to lack of histologic studies or absence of data which would permit the definite exclusion of coexisting thiamin deficiency.[19,20] As a complication of the hemorrhagic tendencies of scorbutic patients, bloody pericardial effusions may occur. Definite myocardial abnormalities have been associated with vitamin C deficiencies in animals. These include fatty and other degenerative lesions as well as nonspecific valvulitis, endocarditis and myocarditis.[21–24]

In spite of a recent interest in vitamin E in heart disease, no instances of cardiac disease due to deficiency of this vitamin have been reported in man. Animal studies have revealed fibrotic or active inflammatory lesions following deprivation of this vitamin.[25,26] Electrocardiographic studies in vitamin E–deficient cattle revealed a progressive decrease in QRS amplitude with an increasing delay in conduction.[27]

Vitamins A and D are stored in such excess that many months of total deprivation are required to induce deficiency states. Accordingly, deficiencies of the water-soluble vitamins appear much earlier. In those cases in which the lack of either of these vitamins has been blamed for cardiac lesions, the coexistence of thiamin and other deficiency states cannot be eliminated. Animal experiments have failed to reveal changes in the electrocardiogram of rats rendered deficient in either of these food elements.[28] It is of interest, however, that calcification of the myocardium and cardiac valves was histologically demonstrated in a thirty-two year old woman who suffered from vitamin D intoxication.[29]

NUTRITIONAL HEART DISEASE

The effects on the heart of malnutrition and starvation include reduction in muscle mass, followed by variable evidence of myocardial degeneration and brown atrophy.[30] In Africa at least two types of nutritional heart disease have been noted. One is myocardial degeneration and electrocardiographic abnormalities in association with kwashiorkor.[31] This deficiency state is apparently due primarily to protein lack, particularly complete proteins, rather than the deficiency of any single amino acid. Most, if not all, patients suffer from generalized chronic dietary deficiency. The prognosis is good if treated early enough, although the extent of the process at the time of diagnosis and the continuation of adequate nutrition are both of vital significance in determining the future of any patient with kwashiorkor.

A second type of "deficiency" heart disease has been described by Gillanders.[32,33] This syndrome, quite commonly encountered in the Bantu, is characterized by generalized cardiomegaly, gallop rhythm, coexistent liver disease and marked edema. The extent of the latter might be judged by the notation that most patients had chemosis and ascites, almost half had bilateral hydrarthrosis of the knee and one-fifth of the patients had bilateral hydrocele. Of sixty-six patients, all but six have shown histologic evidence of liver disease. These alterations included passive congestion and distention of the central lobular sinusoids with variable atrophy of the surrounding liver cells and slight fibrosis. Additionally, there was microscopic evidence of primary liver disease in practically all patients. The hepatic lesions were considered to be those of chronic malnutrition.

Endomyocardial Fibrosis: In addition to the aforementioned, two somewhat similar clinical syndromes have been reported. The endomyocardial fibrosis encountered by Davies[34,35] in Uganda and by Bedford, Evans and Konstam[36] in East and West Africans stationed in the Middle East appear to have much in common. Both processes are characterized by endomyocardial fibrosis which may be quite extensive and by predilection for young adults. However, the syndromes differ in that Davies emphasizes the frequency and significance of atrioventricular valvular insufficiency and of extensive endocardial fibrosis, occasionally leading to partial ventricular obliteration, while Bedford, Evans and Konstam note the frequency of aortic hypoplasia in their patients. In each instance the specific cause has not been demonstrated but impaired nutrition was a possible contributory factor.

Both groups of patients consisted of young adults who experienced a relatively short clinical course marked by rather poor response to all forms of therapy and a high mortality rate. However, significant differences were noted in that Davies' patients, subsequently shown by postmortem examination studies to have more extensive endocardial fibrosis, usually presented the clinical picture of atrioventricular valve insufficiency, particularly mitral. A minority exhibited the features of nonspecific myocardial failure and had an even poorer prognosis. Bedford's series, on the other hand, uniformly presented the clinical features of myocardial insufficiency, frequently with low blood pressure, diminution in pulse pressure and roentgenographic findings consistent with aortic hypoplasia.

Cardiovascular Collagenosis: To complicate matters further, still another entity has been reported from Africa by Becker and co-workers.[37] Entitled cardiovascular collagenosis with parietal thrombosis, this syndrome is characterized by mural thrombosis and by myocardial

and generalized connective tissue lesions similar to those found in the diffuse collagen diseases. The clinical picture and course are typical only of severe and rapidly progressive congestive heart failure in the absence of common etiologic factors. However, in many instances dyspnea, tachycardia, hepatomegaly and serous cavity effusions were disproportionately severe when compared to the degree of congestive heart failure present. The authors made no mention of nutrition in their report, but indicate that of those patients in whom appropriate data were available, anemia and hypoproteinemia occurred in a significant number.

Each of the cited reports from Africa describes a somewhat different syndrome. However, review of the cases included in various series indicates that differentiation is not absolute. Thus a small number of any one author's cases may meet the diagnostic criteria of another syndrome, described by a different investigator. Significantly, endomyocardial fibrosis has been reported from other areas. In America, Smith and Furth[38] described five patients whose clinical course and autopsy findings were similar to those described by Davies. Each of these patients gave a history of dietary deficiencies. Gray[39] reported two similar cases which he had encountered in England. Both patients were Europeans who had spent considerable time in West Africa and in whom there was no evidence of malnutrition. Similarly McKusick[40] reported extensive endocardial fibrosis in the apparent absence of impaired nutrition. Even allowing for lack of recognition, however, it would appear that the syndromes reported from Africa are only rarely met with in other areas.

Etiology of Reported Cases: The relationship between the cases reported herein and nutritional heart disease other than beriberi is conjectural. Although our patients must have suffered from multiple subclinical deficiencies, one cannot conclude that their cardiac disease was due to these multiple deficiencies and not to thiamin deprivation. Rather, we must accept the existence in the alcoholic of a broad spectrum of clinical syndromes of cardiac insufficiency due to general malnutrition. It is almost impossible for man to have a purely single nutritional deficiency. Many factors, many unknown, are probably also deficient. We must, therefore, concede the possibility of etiologic significance of a deficiency or of deficiencies other than thiamin. Only further observation and investigation will clarify the situation. The persistence of clinical, electrocardiographic and roentgenographic indications of heart disease after adequate therapy has been noted in some of the nutritional states reported from Africa as well as in beriberi. In the latter instance it is uncommon and raises the possibility of a deficiency other than, or in addition to, thiamin, although irreversibility in some cases must be merely a function of duration and extent of thiamin deprivation.

ALCOHOL AND CARDIAC DISEASE

Almost 100 years ago a localized form of cirrhosis, occurring in the myocardial wall and trabeculae carneae in the absence of impaired coronary circulation, was ascribed to chronic alcoholism.[41] More recently Eliaser[42] reported the existence of alcoholic myocardosis unrelated to hepatic cirrhosis or vitamin deficiency. In this syndrome there were no manifestations of cardiac disease other than electrocardiographic abnormalities indicative of altered left ventricular repolarization. These aberrations disappeared after several days of abstinence from alcohol. Brigden,[43] in a discussion of the noncoronary cardiomyopathies, included a group of chronic alcoholics in whom cardiac disease was attributed to excessive alcohol ingestion. The patients were uniformly well nourished, failed to present evidence of hyperkinetic circulatory changes and did not respond significantly to large doses of thiamin. Although their initial response to treatment was good, they experienced repeated episodes of congestive heart failure and showed a diminishing response to therapy.

For some time alcoholic cardiomyopathy has been of concern to Evans,[44] who described distinctive electrocardiographic findings in this syndrome. These consist of dimpled, cloven or spinous T waves. Multiple ectopic contractions of multifocal origin, occurring in the presence of moderate tachycardia, are also considered to be of diagnostic value. The late clinical picture described by this author is one of high output cardiac failure. Discontinuation of alcohol early in the course of the disease will lead to reversal of clinical and electrocardiographic abnormalities. In Evans' experience supplemental thiamin therapy is unnecessary.

The clinical syndrome of the patients presented was prominently colored by the severe alcoholism in every instance. In addition,

therapy was associated with elimination of alcoholic intake. To focus attention on the dietary and other factors and to eliminate the alcohol completely as a contributing factor is certainly erroneous. The possible etiologic toxic influence of this agent on the myocardium is considerable and can be as important as it is in hepatic degenerative disease. It cannot be denied that all patients described in this report had been drinking large quantities of alcohol each day for a long period of time. Also, during therapy alcohol ingestion was stopped. Therefore, the only two definite findings in all patients pertain to alcohol, whereas the extent of malnutrition or significance of change in nutrition or vitamin therapy were not clearly defined. It would appear that the role of alcohol in the production of the heart disease should not be ignored. Malnutrition, infection and other factors may have contributed to the clinical state. This association of heart disease with alcoholism has been noted for many years at the Charity Hospital, but the cause and effect relationship has been no more definite than in these patients although it was considered to be probable. This relationship needs further study and clarification.

Summary

The frequent coexistence of malnutrition and heart disease with an obscure cause is a worldwide phenomenon. In only a few instances has a causal relationship between these entities been accepted, e.g., kwashiorkor, beriberi. Nevertheless, circumstances suggest similar instances which demand further study.

Consideration must also be given to the possibility that alcohol *per se* may have a direct toxic effect on the heart.

To illustrate these problems further, eight cases are reviewed. The clinical picture and course exhibited by these patients ranged from that of classic beriberi heart disease to typical nonspecific heart failure. In every instance alcoholism was a prominent feature of the clinical syndrome.

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Cardiovascular Findings in Children with Sickle Cell Anemia*

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CHILDREN with sickle cell anemia often present evidence of cardiovascular involvement. Heart murmurs, roentgenographic evidence of cardiac enlargement, "flooded" lung fields and electrocardiographic abnormalities may be noted. Right heart catheterizations were done in seven Negro children having hemoglobin S in excess of 90 per cent and hematocrits ranging from 18 to 27 per cent. The clinical, laboratory and hemodynamic findings are reported.

CASE HISTORIES

CASE 1. This six year old girl (D. K.) had exertional dyspnea and fatigue since early childhood. She had a history of recurrent abdominal pain and of syncope on several occasions. Growth had been slow and on admisson to school her weight was 34 pounds. Routine physical examination at that time revealed a heart murmur and in the course of her cardiac investigation she was discovered to have sickle cell anemia.

CASE 2. This eight year old girl (V. H.) was discovered to have sickle cell anemia at the age of four when she was investigated for exertional dyspnea and fatigue. She had recurrent tonsillitis and numerous upper respiratory infections. At the age of seven pneumonia developed and a heart murmur was noted at that time.

CASE 3. This nine year old girl (C. W.) had exertional dyspnea and fatigue from early childhood. She was discovered to have sickle cell anemia at the age of five for which she was given a transfusion. Cardiomegaly and a heart murmur were noted at that time. The severity of the anemia necessitated a number of blood transfusions over the next several years. She had frequent bouts of tonsillitis, otitis media and upper respiratory infections. Pain in the abdomen and lower extremities occurred intermittently.

CASE 4. This twelve year old girl (J. E.) had a history of weakness, malaise, exertional dyspnea and fatigue from early childhood. Upper respiratory infections were frequent. There were occasional attacks of left upper quadrant pain and abdominal colic. Following an initial blood transfusion at the age of six she received a number of transfusions over the next several years.

CASE 5. This thirteen year old girl (M. P.) was found to have sickle cell anemia at the age of nineteen months and during the next few years received a number of blood transfusions. Exertional dyspnea and fatigue were present from early childhood. A heart murmur was first detected at two years of age and slight cardiomegaly at the age of three. She had frequent upper respiratory infections including pneumonia on two occasions. Epigastric pain occurred once or twice weekly and was usually brought on by moderate exercise. At the age of twelve gallstones were found. She was given transfusions until the hemoglobin rose from 6.3 to 10.9 gm. per cent prior to surgery and she underwent a cholecystectomy without incident.

CASE 6. This ten-year old boy (G. M.) was hospitalized for convulsions at the age of six weeks when he was found to have anemia. At one year of age he was hospitalized for meningitis. Sickle cell anemia was diagnosed at this time. Over the next few years he was given numerous blood transfusions. His activity was markedly limited because of exertional dyspnea and fatigue.

CASE 7. This sixteen year old girl (B. K.) was found to have sickle cell anemia on a routine examination after it had previously been discovered that her younger sister (Case 1) had sickle cell anemia. Mild exertional dyspnea, easy fatigability and intermittent leg pains had been present from early childhood. These symptoms had increased moderately with the onset of her menses at the age of fifteen.

* From the United Hostesses Cardio-Respiratory Laboratory, Cedars of Lebanon Hospital and the Los Angeles Board of Education and Parent-Teacher Cardiac Clinics. This study was supported in part by the United Hostesses.

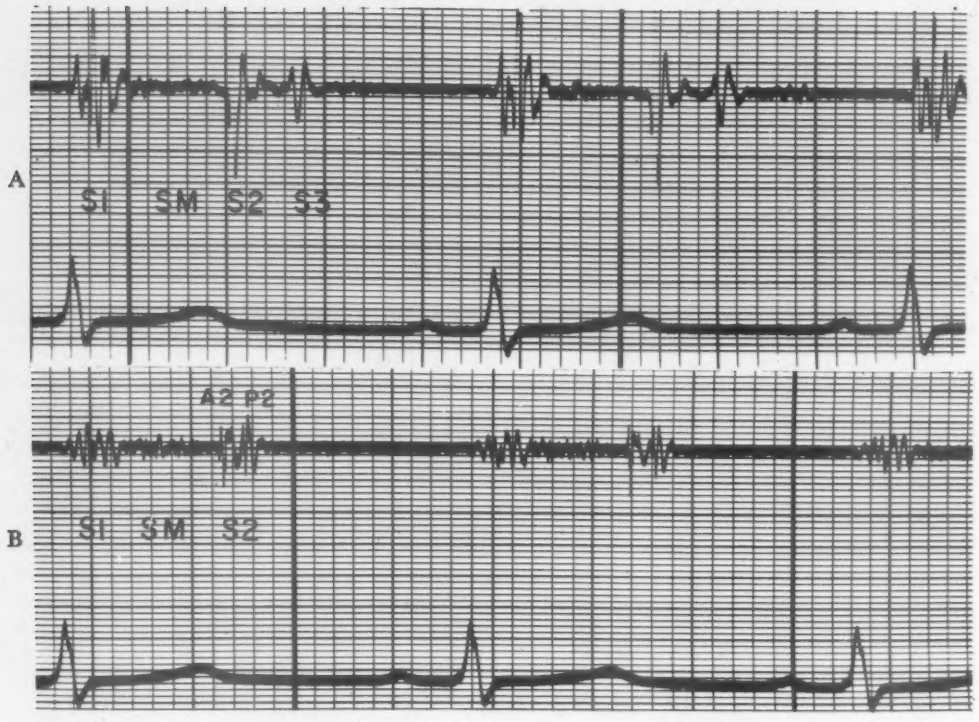

FIG. 1. Case 6. A, the phonocardiogram at the apex shows a third heart sound (S3) 0.13 second after the onset of the second heart sound (S2). A systolic murmur (SM) is noted in this area. B, the phonocardiogram over the pulmonic area shows a split second sound (S2) with the split measuring 0.045 second between the aortic (A2) and pulmonic (P2) components. A more prominent systolic murmur (SM) is present in this area.

CLINICAL FINDINGS

General: These patients were underweight and thin-chested, with long thin extremities and slender fingers. The sclerae were icteric in three of the seven patients; cervical adenopathy was present in one. Three patients had hepatomegaly and splenomegaly. Ulceration of the lower extremities was noted in one patient.

Cardiovascular Findings: Six patients had significant cardiomegaly. In three patients a prominent apical impulse was felt at the left anterior axillary line in the fifth or sixth interspace. A left parasternal lift was frequently felt. There were no thrills. The first heart sound was slightly accentuated at the apex in four patients. The second sound over the pulmonic area was widely split with the split ranging from 0.03 to 0.05 second during the expiratory phase of normal respiration (Fig. 1A). During normal inspiration the split increased by 0.01 second or less. Both components of the second heart sound were prominent. Five patients had a distinct "filling" third heart sound in early or mid-diastole which was best heard at the apex (Fig. 1B). An early systolic ejection click was present over the pulmonic area in one patient. All of the patients had blowing systolic murmurs of grade II to III intensity which were maximal over the second or third interspace on the left (Fig. 1A). The murmurs were widely transmitted over the precordium. No diastolic murmurs were heard. The heart rate varied between 90 and 100 beats per minute. Systemic blood pressures were normal in all instances.

Laboratory Findings: The hemoglobins ranged from 6.3 to 9.5 gm. per cent and the hematocrit readings from 18 to 27 volumes per cent (Table I). Electrophoretic studies revealed sickle cell hemoglobin in excess of 90 per cent in every case. Blood volume studies employing radioactive iodinated human serum albumin (RISA) were performed in six of these patients. The total blood volume was markedly increased in five and at the upper limit of normal in one (Table I). The plasma volume was greatly increased while the red cell mass and hematocrit were very low.

Roentgenography and Fluoroscopy: There was diffuse cardiomegaly in all patients, the enlargement being moderate in six (Fig. 2) and slight

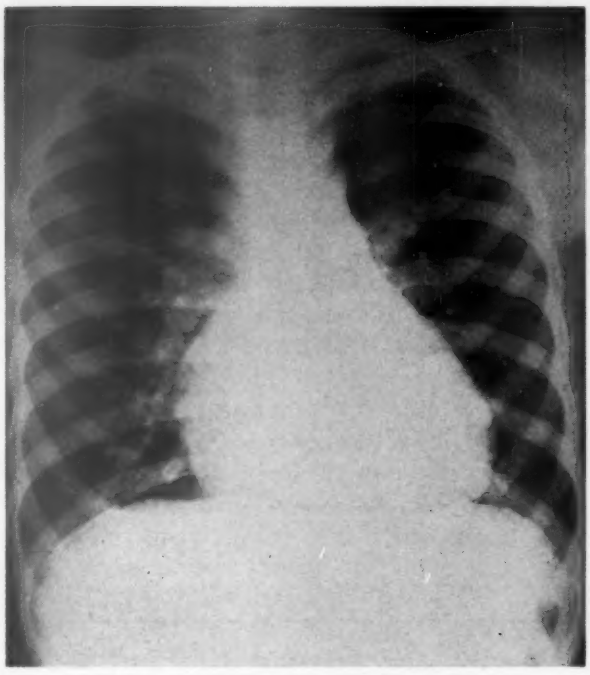

FIG. 2. Case 2. The chest roentgenogram shows a globular, diffusely enlarged heart. The main pulmonary artery segment is prominent and there is a striking increase in the pulmonary vascularity.

in one. In four patients the cardiac contour was globular. The pulmonary artery was slightly enlarged in six patients and moderately enlarged in one. The pulmonary vascular markings were moderately increased in three patients and slightly increased in three others. Fluoroscopically the pulmonary artery showed increased expansile pulsations.

Electrocardiography and Vectorcardiography: Right ventricular hypertrophy was present in one patient. In three patients an rsR′ configuration was present in V_1 and the right precordial leads, but the QRS duration was less than 0.09 second. In one patient the T waves were deeply inverted in V_1 to V_6; flattened T waves were present in leads I and aVL and low T waves in leads II, III and aVF. In three patients tall, peaked T waves and slightly elevated S-T segments were present in leads V_4 to V_6 together with high QRS voltages. In these patients the S wave in V_1 plus R wave in V_5 totalled 50 mv. or more. The mean QRS axis in the frontal plane ranged from +30° to +60° in six patients and in the patient with right ventricular hypertrophy was +90°. The P-R and Q-T intervals were normal.

Vectorcardiograms were taken employing the cube and Frank systems. In one patient a figure of eight loop was inscribed in the horizontal plane which was indicative of right ventricular hypertrophy. Two patients showed incomplete right bundle branch block with the terminal vectors delayed and directed to the right, posteriorly and slightly superiorly. Nonspecific T wave abnormalities were noted in one patient.

Hemodynamic Studies

Method: The patients were mildly sedated and locally anesthetized. The catheter was advanced through the superior vena cava, right atrium, right ventricle and main pulmonary artery to the peripheral pulmonary artery. In two patients the coronary sinus also was entered. Pressures were recorded in these sites via a Statham pressure transducer type P-23A and Sanborn direct-writing Viso Cardiette. Blood samples were obtained from these sites and were analyzed for oxygen content by a modification of the Van Slyke and Neill technic.[1] Arterial pressures and blood samples were obtained via a Riley needle inserted into the brachial artery. The above studies were performed while the patient was breathing ambient air in the resting state. With the catheter in the main pulmonary artery and the Riley needle in the brachial artery the patients

TABLE I

Blood Findings, Blood Volumes and Cardiac Outputs in Seven Cases of Sickle Cell Anemia

Patient No.	Hemoglobin (gm. %)	Red Cell Mass (ml./kg.)	Blood Volume (ml./kg.)	Plasma Volume (ml./kg.)	Cardiac Index (L./min./m²BSA)	Stroke Index (ml./beat/m²BSA)	Heart Rate (per min.)
1	8.4	—	—	—	7.2	77	94
2	7.4	18.3	90.5	72.2	8.2	91	90
3	6.5	18.5	86.8	68.3	7.2	78	92
4	7.0	18.6	67.7	49.1	4.6	48	96
5	6.3	22.6	119.8	97.2	11.7	117	100
6	7.4	28.8	109.5	80.7	8.5	85	100
7	9.5	31.6	91.4	59.8	3.8	42	90

TABLE II
Intracardiac Pressures and Pulmonary Vascular Resistances in Seven Cases of Sickle Cell Anemia

Case No.	Age	Pressures (mm. Hg)					Total Pulmonary Vascular Resistances dynes sec. cm.$^{-5}$	
		RA Rest	RV Rest	MPA Rest	MPA Exercise	PPA Rest	Rest	Exercise
1	6	7/4	35/5	28/12	29/13	7/4	234	—
2	8	8/5	35/6	27/11	29/11	—	156	120
3	9	8/4	30/6	27/12	27/12	11/6	172	106
4	12	5/2	27/3	25/13	30/14	12/6	226	143
5	13	5/3	23/3	22/10	28/18	—	94	84
6	10	5/1	30/4	28/9	—	10/4	136	—
7	16	7/2	32/2	29/8	30/8	10/5	222	—

TABLE III
Arterial and Venous Oxygen Saturations in Seven Cases of Sickle Cell Anemia

Case No.	Per Cent of Oxygen Saturation Breathing Ambient Air					Per Cent of Oxygen Saturation Breathing 100% O_2	
	MPA		Brachial Artery		Coronary Sinus	MPA Rest	Brachial Artery Rest
	Rest	Exercise	Rest	Exercise			
1	63.3	61.8	86.8	86.3	31	68.3	90.5
2	59.5	59.5	76.5	81.2	—	69.3	88.6
3	58.8	51.9	79.3	79.3	—	63.8	85.8
4	67.3	59.9	88.5	90.2	39.5	69.2	91.2
5	59.9	59.8	80.2	80.9	—	—	89.2
6	59.2	—	78.8	—	—	—	—
7	64.8	37.7	89.0	88.4	—	75.3	91.0

exercised for five minutes by pedalling a bicycle in the recumbent position and pressures and samples were taken. After a period of rest the patients inhaled 100 per cent oxygen for periods varying from fifteen to twenty minutes. Simultaneous samples were drawn from the main pulmonary artery and from the brachial artery and were analyzed for oxygen content. Mean pressures at rest and with exercise were calculated by planimetry and total pulmonary vascular resistances were determined. Resting oxygen consumptions were determined by collecting samples of expired air in Douglas bags with subsequent Haldane analysis. Cardiac outputs were determined by the direct Fick principle. In two patients the Valsalva maneuver was performed.

Results: Normal pressures were recorded in the superior vena cava and right atrium (Table II). Slight elevations of the right ventricular systolic pressures were noted in some instances (Table II). The end diastolic pressures in the right ventricle were normal.

Pulmonary artery systolic pressures at rest were below 30 mm. Hg in every case. Slight systolic gradients were noted in some instances between the right ventricular and pulmonary artery pressures. There were no significant increases in pulmonary artery pressures with exercise. The peripheral pulmonary arterial "wedge" pressures were normal in all of the patients in whom they were obtained. The total pulmonary vascular resistances were normal or low at rest and with exercise (Table II).

The resting cardiac indices varied from 3.8 to 11.7 L./min./m²BSA (Table I). The lowest cardiac index (3.8) was found in the patient with the highest hemoglobin (9.5 gm. per cent). Five of the seven patients had marked elevation of their stroke indices; one was high normal and one was normal. The heart rates ranged from 90 to 100 beats per minute.

Arterial oxygen unsaturation was present in all patients while at rest and breathing room air, the saturations ranging from 76.5 to 89.0 per cent (Table III). No significant changes in systemic arterial oxygen saturations were noted after exercise in five of six patients in the present series. Resting pulmonary artery oxygen saturations ranged from 58.8 to 67.3 per cent (Table III). Significant falls in pulmonary artery oxygen saturations occurred in three patients during exercise, two of these patients having the lowest cardiac and stroke indices. In three patients there were no significant changes in the pulmonary artery oxygen saturations with exercise. Blood samples from the coronary sinus in two patients revealed oxygen saturations of 31 and 39.5 per cent, respectively.

Arterial oxygen saturations increased in all patients on breathing 100 per cent oxygen (Table III). In no instance, however, was a full arterial oxygen saturation reached. In general, mixed venous samples from the pulmonary artery showed comparable increases in oxygen saturation on breathing 100 per cent oxygen (Table III).

An abnormal response to the *Valsalva maneuver* was observed in the two patients in whom it was measured. No significant fall in the systolic pressure or pulse pressure occurred during phase one of the period of forced straining and the overshoot was minimal and unaccompanied by bradycardia in phase four.

Comments

AUSCULTATION

Systolic Murmur: Systolic murmurs were heard in all of these children with sickle cell anemia. As is well known, systolic murmurs frequently may be heard in normal children. By means of intracardiac phonocardiography during right heart catheterization, Feruglio[2] demonstrated a systolic murmur within the pulmonary artery in all patients including those with normal catheterization findings. Simultaneous phonocardiograms from the overlying anterior chest wall, however, failed to reveal a systolic murmur in over 50 per cent of these patients. In the current study a grade II to III systolic murmur was heard in every patient. Systolic murmurs have been noted frequently in severe anemias of various causes[3–5] and have been reported as being most prominent either at the apex[6] or of equal prominence at the apex and base of the heart.[7]

In all of these children with sickle cell anemia the murmur was maximal over the upper left sternal border. Since the character and location of the murmur were similar to those observed in interatrial septal defect, this condition was often suspected. By means of intracardiac phonocardiography Feruglio[2,8] has shown that in interatrial septal defects the systolic murmur is localized to the pulmonary artery. This has been explained on the basis of the increased blood flow into this vessel which occurs in this condition. In these children with sickle cell anemia the cardiac and stroke indices were high (Table I) and it is suggested that this increased flow into the pulmonary artery was responsible for the murmur.

Third Heart Sound: Prominent third "filling" heart sounds in early or mid-diastole were heard in five of the seven patients in this series, an incidence similar to that reported by Klinefelter.[5] In Hunter's[3] series of nonsickle cell anemias a third heart sound was heard in eight of thirty-four patients but of these six were in congestive heart failure. All of these patients were over thirty years of age, a time when such sounds are apt to have more pathologic significance than in children in whom a third heart sound frequently is a normal finding. None of the patients with sickle cell anemia was in congestive failure and this could not have been responsible for the third heart sound.

Second Heart Sound: The second sound over the pulmonic area was split in all seven patients, with both components prominent. Accentuation of P2 has been noted previously in sickle cell anemia[4,5] and in some instances has been attributed to pulmonary hypertension.[13] In the present study the pulmonary artery pressures were normal in all cases. Since the aortic component of the second sound usually was equally prominent, other factors, such as the thinness of the chest wall or the hyperkinetic state, may have been involved.

In these patients with sickle cell anemia the split in the second sound ranged from 0.03 to 0.05 second during the expiratory phase of normal respiration and increased 0.01 second or less during inspiration. No significant differences in the splitting of P2 were found among the three patients with incomplete right bundle branch block and those without it. It has been pointed out by Leatham and Towers[14] that in normal patients the second sound is single or split by 0.03 second or less in the expiratory phase with the split widening to 0.05 twenty-seven patients the ST-T abnormalities

second on an average on inspiration. In patients with atrial septal defects, however, Leatham and Gray[10] found wide splitting of P2 in the expiratory phase of normal respiration with little or no increase in the inspiratory phase and suggested this as a diagnostic sign of this condition. In these patients with sickle cell anemia the split in the second sound tended to be greater than normal during expiration but the increase in the split of the second sound during inspiration was less than normal. The majority had significantly increased stroke indices (Table 1). Presumably, the filling of the right ventricle was greater than normal during expiration and the increment in filling with inspiration was less than normal.

Ejection Click: A pulmonary systolic ejection click was present in one patient (Case 5) who had moderate enlargement of the pulmonary artery. Pulmonary ejection clicks are common in pulmonary hypertension, mild pulmonic stenosis, idiopathic dilatation of the pulmonary artery,[9,11] and in some cases of atrial septal defect in the absence of pulmonary hypertension.[9,10] The pulmonary ejection click has been explained on the basis of sudden distention of a dilated pulmonary artery.[12] The presence of a markedly increased stroke index in Case 5 in association with the enlarged pulmonary artery could account for the ejection click despite the absence of pulmonary hypertension.

ROENTGENOGRAPHY AND FLUOROSCOPY

Heart: Radiologically, diffuse cardiac enlargement has been commonly observed in sickle cell anemia,[5,15–17] the heart often tending to be globular in shape.[16,18] A typical mitral configuration of rheumatic heart disease was reported by Henderson[19] in one-third of the patients who had cardiomegaly. Leight et al.[20] observed disproportionate left atrial enlargement fluoroscopically in four of thirteen patients, but one was believed to have rheumatic heart disease. Other observers have not reported disproportionate enlargement of the left atrium.[5,21] All of the patients in our series had diffuse cardiomegaly and most had globular-shaped hearts; none showed disporportionate chamber enlargement. Since there was no evidence of mitral valvular disease or intracardiac septal defect on cardiac catheterization, it is our opinion that these radiologic changes were on the basis of the sickle cell anemia.

Pulmonary Vasculature: An enlarged pulmonary artery segment has been reported in sickle cell anemia[5,16,21] and was present in all seven patients. Fluoroscopically, the pulmonary artery was enlarged and was observed to pulsate forcibly. Increased pulmonary vascular markings were present in six of the seven patients. It is of interest in this respect that several investigators[22,23] have reported a decrease in vital capacity in severe chronic anemia. Blumgart and Altschule[22] suggested that the decrease in vital capacity was similar to that which ocurred with pulmonary congestion or edema. In the present series, however, no elevation of the wedge pressure was found in any instance and it is our opinion that the increased pulmonary vascular markings were on on the basis of increased pulmonary blood volume in the absence of congestive heart failure.

ELECTROCARDIOGRAPHY AND VECTORCARDIOGRAPHY

Various electrocardiographic abnormalities have been reported in sickle cell anemia. Prolongation of the P-R interval, nonspecific changes in the S-T segment and the T wave, left ventricular hypertrophy and strain and incomplete right bundle branch block have been described.

P-R Interval: Prolongation of the P-R interval was reported by Klinefelter[5] in six of twelve cases and it was postulated that this was due to increased vagal tone. Lindo and Doctor[24] found a prolonged P-R interval in 29 per cent of patients with sickle cell anemia while Winsor and Burch[21] reported slight prolongation in 12 per cent of cases. In the current series the P-R interval was normal in all patients according to the criteria of Ashman and Hull.[25]

ST-T Changes: Nonspecific S-T changes have been reported in sickle cell anemia. Lindo and Doctor[24] noted low, inverted or notched T waves in 56 per cent of patients and depressed S-T segments in 26 per cent. Nonspecific T wave changes were found in 20 per cent of the patients reported by Winsor and Burch[21] while Henderson[19] found evidence of myocardial ischemia in twelve of thirty patients, with three of these patients developing positive T waves following blood transfusion. In a study of one hundred patients with severe chronic anemias of various causes, Sanghvi et al.[26] noted S-T segment depression in fifty-four cases and inverted T waves in sixty-two. In

persisted despite subsequent cure of the anemia. Sanghvi et al.[26] attributed the persistence of the electrocardiographic abnormalities in these nonsicklemic patients to persistent and probably irreversible cardiac changes as a result of prolonged hypoxemia.

In our patients with sickle cell anemia S-T segment depression was not encountered in a single instance. Three patients, however, had slight elevation of the S-T segment in V_4 to V_6 together with tall, peaked T waves. In one patient deeply inverted T waves were present in V_1 through V_6.

Left Ventricular Hypertrophy: This finding was reported by Leight et al.[20] in four of thirteen cases of sickle cell anemia while Lindo and Doctor[24] noted two cases of left ventricular strain in thirty-four patients with abnormal electrocardiograms. High QRS voltages over the left precordial leads were found in three of the seven patients in our series. The significance of these high precordial QRS voltages is uncertain. Sokolow and Friedlander[27] have pointed out that high left precordial voltages in children do not necessarily indicate left ventricular hypertrophy since such high QRS voltages may occur normally. In addition to the high QRS voltage these three patients showed S-T segment elevation and tall, peaked T waves in leads V_4 through V_6. The S-T elevation in association with the high voltage QRS in these leads is suggestive of diastolic overloading of the left ventricle as described by Cabrera and Monroy.[28] Sodi-Pallares et al.,[29] however, have pointed out the diagnostic limitations of this finding since it may be seen in the absence of diastolic overloading.

Electrical Axis: The QRS axis ranged from $+30°$ to $+60°$ with the exception of the one patient with right ventricular hypertrophy in whom the axis was $+90°$. Winsor and Burch[21] reported one case of right axis deviation in a series of twenty-five patients with sickle cell anemia, but clinically it was believed that the patient had experienced a recent pulmonary infarction. The electrical axis of the other patients in their series ranged from 0 to $+72°$ with the average QRS axis $+49.5°$, and the average age thirteen years. In our series the average QRS axis was $+48°$ and the average age ten years. In this age group a more positive axis might be expected.

Right Ventricular Changes: Incomplete right bundle branch block was found in three of the seven patients. To our knowledge only one case of incomplete right bundle branch block has been reported previously.[20] Right ventricular hypertrophy was present in one patient, a finding to our knowledge not previously reported in children with sickle cell anemia. Right ventricular hypertrophy at necropsy has been described by Yater and Hansmann[31] in two patients with sickle cell anemia who died in right ventricular failure. The cor pulmonale apparently was due to widespread, disseminated thrombotic lesions in small pulmonary arteries with thickening of the walls and narrowing of the lumen in these vessels. Mild or moderate pulmonary arteritis and thrombosis was found at necropsy in six of nine patients studied by Winsor and Burch[21] but these authors did not consider the pulmonary lesions which were encountered of sufficient severity to produce cor pulmonale. Klinefelter,[5] in a necropsy study of eleven cases of sickle cell anemia, found no striking changes in the pulmonary vasculature.

Vectorcardiography: Vectorcardiograms were taken in all seven patients. Three of the patients had abnormal vectorcardiograms. In the patient with electrocardiographic evidence of right ventricular hypertrophy a figure of eight loop was inscribed in the horizontal plane. Terminal delays in the spread of the depolarization wave were encountered in two other patients with the terminal vector forces being directed to the right and posteriorly.

HEMODYNAMIC STUDIES

Pulmonary Artery Pressure: In the current series the pressures in the pulmonary artery were not elevated at rest or with exercise (Table II). Although slight systolic gradients between the right ventricle and pulmonary artery were noted in some instances, this was not attributed to valvular pulmonic stenosis but to the increased flow. Sproule et al.[22] found normal pulmonary artery pressures at rest in four of five patients with sickle cell anemia. Leight et al.[20] found normal pulmonary artery pressures at rest in all but two of thirteen patients with sickle cell anemia, one exception occurring in a patient who was believed to have cor pulmonale and the other in a patient with concurrent rheumatic heart disease. On exercise, however, significant elevation of pulmonary artery pressure developed in four of ten patients in Leight's series.

Vascular Resistance: The pulmonary vascular resistance was normal or low in all of the seven patients at rest and with exercise (Table II).

Reduced pulmonary and peripheral vascular resistances in severe anemia have been reported by various authors[32–34] and the suggestion has been made that the associated hypervolemia is a contributing factor. Ferguson et al.,[35] however, demonstrated that hypervolemia without anemia does not lower total peripheral resistance in dogs. Fowler et al.[36] found that anemic dogs with and without hypervolemia showed comparable degrees of diminution in total peripheral resistance and this led them to suggest that other factors were responsible for the low resistance. Lowering of peripheral vascular resistance in severe anemia has been attributed in part to a reduction in blood viscosity. In these patients with sickle cell anemia the total blood volume was markedly elevated while the red cell mass was considerably decreased (Table I). The resultant reduction in viscosity of the blood may have been a factor in reducing the vascular resistance. Sproule et al.[23] noted normal pulmonary vascular resistances in the patients in their series, in the presence of appreciably elevated cardiac indices. These authors suggested that the total peripheral vascular resistance might be lowered on the basis of extensive arteriovenous anastomoses.

Cardiac Output: The cardiac indices were elevated in six of the seven patients (Table I). Increases in cardiac output in nonsickle cell anemias have been reported by Brannon et al.[33] and by Sharpey-Schafer.[32] The latter author noted an increase in right atrial pressure in most cases of severe anemia. Leight et al.,[20] however, found normal right atrial pressures in patients with sickle cell anemia and Bishop et al.[34] found lack of definite evidence of raised filling pressure on either side of the heart in patients with chronic severe anemias from various causes. No elevation of the wedge pressure or of the right ventricular end diastolic pressure was found in our series (Table II). The heart rates tended to be normal or only slightly increased despite the severity of the anemia (Table I). The greatly elevated cardiac indices were achieved therefore primarily by an increase in the stroke indices. Experimental evidence in support of this was provided by Rushmer[37] in a series of animal experiments in which he demonstrated that there may be a change in the diastolic distensibility of the myocardium without a corresponding change in effective filling pressure.

Valsalva Maneuver: The arterial response to the Valsalva maneuver was abnormal. During the straining period, when intrapulmonary pressure was increased, there was no significant drop in arterial systolic pressure or in pulse pressure as occurs normally.[38] During phase 4 the overshoot was minimal and was unaccompanied by bradycardia. This type of response is somewhat suggestive of that observed with congestive heart failure,[38] but the finding of a normal wedge pressure and of a normal end diastolic pressure in the right ventricle were against the presence of either left or right heart failure. It is suggested that this abnormal Valsalva response was due to increased pulmonary vascular blood volume in association with the large total blood volume which was found in these patients (Table I).

Oxygen Saturation: Arterial oxygen unsaturation was present in all patients in the present series (Table III). Similar arterial oxygen unsaturation has been reported by others in sickle cell anemia[20,23,40–45] as well as in other chronic anemias.[46,47] No significant changes in arterial saturation were noted with exercise in five of the six patients (Table III) although Leight et al.[20] noted a fall in the arterial oxygen saturation during exercise in five of twelve patients. Mixed venous blood samples obtained from the pulmonary artery in the present study had oxygen saturations which ranged from 58.8 to 67.3 per cent. Since the arterial oxygen saturations were significantly decreased, the arteriovenous oxygen differences tended to be somewhat less than usual (Table III). Even with exercise three of the patients failed to show a significant decrease in venous oxygen saturation as occurs under normal circumstances.

Oxygen Dissociation Curve: Several suggestions have been advanced to explain the arterial oxygen unsaturation in sickle cell anemia and other anemic states. Abnormalities of the oxyhemaglobin dissociation curve,[39,41,42,44–46] venoarterial shunting in the lungs[23,42] and pulmonary diffusion defects[13] separately or in combination have been suggested. The presence in sickle cell anemia of an abnormal oxyhemoglobin dissociation curve which was shifted to the right was first suggested by Scriver and Waugh.[39] These investigators were of the opinion that the shift of the dissociation curve was not a function of the sickle cell abnormality *per se*, but probably was on the basis of the anemic state, with a decrease in the pH of the red blood cell occurring due to insufficient oxygenation. Fraimow et al.[44] and

Rodman et al.[45] also found displacement of the oxyhemoglobin dissociation curve downward and to the right in patients with sickle cell anemia and likewise suggested that this might be related to a reduction in the pH of the red blood cell. Becklake et al.,[41] in a study of four patients with sickle cell anemia, found the oxygen dissociation curve displaced to the right but attributed this, however, to the serum environment of the cell. Other investigators have observed a rightward shift of the oxygen dissociation curve in various nonsicklemic anemias. Kennedy and Valtis[46] found rightward displacement of the oxyhemoglobin dissociation curve in Addisonian and hypochromic anemia and suggested that lowered red cell pH was a possible contributing factor. They concluded, however, that this was not the only factor since some displacement occurred even when results were corrected to a constant cell pH.

Fowler et al.[42], in a study of ten patients with sickle cell anemia, found an abnormal alveolar-arterial oxygen tension gradient (A-a pO_2 gradient). Ryan and Hickam[47] reported a similar increase in A-a pO_2 gradient in patients with nonsicklemic anemia. Fowler et al.[42] suggested the presence of a hemoglobin defect in which there is a deficient uptake of oxygen by sickle cell hemoglobin at a given oxygen tension, thereby causing a rightward displacement of the oxyhemoglobin dissociation curve. The occurrence of an increased A-a pO_2 gradient also suggests the possibility of a pulmonary diffusion defect. Moser and Shea[13] postulated the occurrence of such a pulmonary diffusion defect on the basis of recurrent pulmonary thromboses and infarctions. They drew attention to the accentuation of the pulmonary second sound and the enlargement of the pulmonary outflow tract as suggestive evidence for associated pulmonary hypertension. In the current series accentuation of P2 and enlargement of the pulmonary artery were found in all cases but cardiac catheterization did not reveal pulmonary hypertension in any instance.

Arteriovenous Shunting: In the present series a rightward shift of the oxyhemoglobin dissociation curve could explain the observed arterial oxygen unsaturation on breathing ambient air but could not explain the oxygen saturations which were present in mixed venous blood. From a review of the oxygen dissociation curves presented by Fraimow et al.[44] and Rodman et al.[45] it would appear that venous oxygen saturations were lower than normal in their cases. Brannon et al.,[33] studying various nonsicklemic anemic patients, found the oxygen saturation of mixed venous blood to be decreased. In our series the mixed venous oxygen saturations were normal or only slightly decreased. Various authors[23] have suggested the occurrence of peripheral arteriovenous shunting of considerable magnitude in sickle cell anemia. Such shunts, if present, could account for the relatively high venous oxygen saturation which were found in our cases particularly after exercise (Table III). The saturations of the coronary sinus samples were of particular interest in this regard, the two samples obtained having oxygen saturations of 31 and 39.5 per cent, respectively. These saturations were somewhat higher than normal[38] and suggested the possibility of coronary arteriovenous shunting.

Venoarterial Shunting: Intrapulmonary venoarterial shunting has been suggested as a cause of arterial oxygen unsaturation. Jensen et al.[43], however, demonstrated that there was an increase in arterial oxygen saturation following transfusion of normal erythrocytes in patients with sickle cell anemia. They concluded, therefore, that there was no significant venous admixture or venoarterial shunting in the lungs. If one assumes the presence of an abnormal oxygen dissociation curve in sickle cell anemia, however, the transfusion of normal cells might well cause a shift of the curve toward normal and thus account for these higher saturations.[44,45] The arterial oxygen saturations on breathing 100 per cent oxygen which were obtained in the present study are noteworthy in this respect, for full arterial saturation was not reached in any instance (Table III). If the arterial unsaturation were entirely explainable on the basis of an abnormal oxygen dissociation curve, one would expect full arterial oxygen saturation on breathing 100 per cent oxygen. Since full arterial saturation was not found in any of the patients in the current series, it is suggested that in these children some degree of intrapulmonary venoarterial shunting was present.

Summary

Cardiovascular findings are described in seven children with sickle cell anemia. Clinically the following features were noted: (1) exertional dyspnea and fatigue; (2) wide fixed splitting of the second heart sound; (3) third "filling" heart sound in five of the seven cases; (4)

systolic murmur of grade II intensity or louder, most prominent over the upper left sternal border; (5) roentgenographic evidence of diffuse cardiomegaly and increased pulmonary vascularity; (6) abnormal electrocardiograms in four cases.

Laboratory findings of note were: (1) hemoglobins from 6.3 to 9.5 gm. per cent and hematocrit readings from 18 to 27 volumes per cent; (2) increased total blood volumes and plasma volumes in five of six patients.

Right heart catheterizations in these patients revealed the following: (1) normal vena caval, right atrial, pulmonary artery and wedged pulmonary artery pressures; (2) normal or low pulmonary vascular resistances at rest and with exercise; (3) cardiac indices averaging twice normal; (4) increased stroke indices; (5) arterial oxygen unsaturation at rest and after breathing 100 per cent oxygen in all cases; (6) relatively small arteriovenous oxygen differences at rest and with exercise; (7) relatively high coronary sinus oxygen saturations; (8) an abnormal Valsalva response.

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Progesterone in Congestive Heart Failure and Hepatic Cirrhosis

Effects on Water and Electrolyte Metabolism*

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IT HAS been sufficiently proved, following the studies of Landau et al.,[1-5] that progesterone causes an increased urinary excretion of nitrogen, sodium and chloride besides inconstant loss of phosphorus and potassium. It was further established that this increased excretion is proportional to the dosage of progesterone and reaches its maximum at a daily dose of 150 mg., while above this dosage no further increase is noted. The natruresis is usually greater than the chloruresis.

Furthermore, it was proved that in order to produce such an effect, it is necessary to have sufficient secretion of aldosterone by the adrenal cortex.

Landau et al., [1-4] in patients with Addison's disease, were able to produce saluretic excretion by progesterone alone if the patients were properly treated for hypoadrenalism by either aldosterone or DCA. In two cases, during acute hypoadrenalism the administration of 150 mg. of progesterone was sufficient to inhibit the sodium retention produced by the intravenous administration of 20 μg. of aldosterone, but not that produced by 40 to 50 μg. of this substance.

The present study was undertaken with the purpose of finding an agent that would be able to antagonize the action of aldosterone in patients with edema without having important side effects.

MATERIAL AND METHOD

Six male patients, whose ages ranged between twenty-seven and sixty-nine years, were used in the present investigation. One patient with hypertensive heart disease without congestive heart failure was used as a control. Four patients had congestive heart failure; three of them had inactive mitral rheumatic disease, associated in one with arteriosclerotic heart disease; the fourth patient had arteriosclerotic heart disease and diabetes mellitus. The sixth patient had cirrhosis of the liver with ascites, hypoproteinemia and edema.

The etiologic diagnosis was based on clinical, electrocardiographic, laboratory and roentgenologic data.

The water, sodium, chloride and potassium balances were studied. The intake of water was free; those of sodium, chloride and potassium were, respectively, 11.6, 13.4 and 41.3 mEq. per day. The loss of water due to perspiration and stools and the electrolyte losses, besides that of urine, were not considered in the calculations.

The study lasted a minimum of sixteen days and a maximum of forty-three, and was divided into three periods: one before, one during and one after the daily intramuscular administration of 100 to 200 mg. of progesterone in oil.

Sodium and potassium were assayed by the flame photometer; the chloride, by means of a modified Volhard-Darrey method.

RESULTS

The changes produced by progesterone in the water and electrolyte metabolism in four patients with congestive heart failure and one control are presented in Tables I (total urinary losses) and II (daily averages).

With one exception (Case 3), the daily averages for water excretion were greater during the second period than during the first and third; in these two periods, the averages were practically identical to each other (Table II). The urinary excretion of sodium, chloride and potassium was also greater in the second period. The increase in the potassium excretion during

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TABLE I
Total Changes in Urinary Electrolyte Excretion Following Progesterone Therapy

Case No.	Age (yr.)	Period	Sodium (mEq.)	Chloride (mEq.)	Potassium (mEq.)	Urine (ml.)	Weight Change (kg.)
1	53	1st	...	...	...	...	...
		2nd	217.3	280.7	252.0	1,250.0	−3.8
		3rd	45.0	161.1	236.6	5,600.0	
2	63	1st	54.2	107.8	95.5	2,480.0	
		2nd	177.4	176.9	144.0	4,225.0	−1.7
		3rd	48.1	80.1	102.5	2,480.0	
3	67	1st	3.8	75.2	101.1	2,200.0	
		2nd	20.9	131.2	207.2	4,620.0	+1.3
		3rd	...	...	...	...	
4	22	1st	5.9	143.0	138.5	3,785.0	
		2nd	187.5	267.7	198.7	4,060.0	−2.1
		3rd	...	...	...	...	
5	50	1st	47.3	134.1	142.2	2,525.0	No change
		2nd	83.2	106.1	84.5	2,400.0	
		3rd	30.8	80.7	103.2	1,980.0	

the second period was smaller than in the previous period; but when related to the increase in sodium excretion, it was even smaller, as one can see from the Na/K ratio.

Case 5, used as a control, showed less striking changes: increase in the excretion of sodium, no changes in that of chloride and a decrease in that of potassium. There was practically no change in the diuresis and the Na/K ratio increased to only three times normal.

The increase of the metabolic changes induced by progesterone is presented in Table III.

There was a substantial loss of body weight during the administration of progesterone in three patients: Case 1, 3.8 kg.; Case 2, 1.7 kg.; Case 4, 2.1 kg. Only one patient (Case 3) had a gain of 1.3 kg. The patient in Case 5 did not show any change in body weight (Table I).

There was an outstanding decrease of edema in three patients; only in Case 3 was there no change.

Case 1 presents features of particular interest. This patient had rheumatic valvular heart disease with completely refractory congestive heart failure; he was in the hospital for more than two months and, in spite of full digitalization, administration of mercurial diuretics and chlorothiazide, there was no decrease of his weight and edema.

As shown in Figure 1 and Table IV, the daily administration of 50 mg. of progesterone slightly changed his diuresis and electrolyte excretions. On the other hand, an increase in the dose of progesterone to 100 mg. for seven days was followed by complete freedom from edema after the seven days. After interruption of hormone therapy, however, the patient started gaining weight again and his sodium and water excretion decreased.

The patient in Case 6 was also studied by the same method. He was a forty-two year old man who had atrophic cirrhosis of the liver, edema, ascites and hypoproteinemia. His data are presented in Tables V (total urinary losses), VI (daily averages) and VII. The increase of metabolic changes induced by progesterone in this case is much more marked than those produced in patients with congestive heart failure.

This patient should be discussed further for two reasons: (1) the different behavior of the water and electrolyte metabolism (Table VII and VIII) with the different sodium intake (more than 80 mEq./day in one period and 10.4

TABLE II

Daily Averages for Water and Electrolyte Excretion Following Progesterone Therapy

Case No.	1st Period	2nd Period	3rd Period
	Sodium (mEq.)		
1	1.1	31.8	6.4
2	10.8	22.2	9.6
3	1.3	3.0	...
4	1.2	37.5	0.9
Average	3.6	23.6	5.6
5 (Control)	7.8	16.1	7.7
	Chloride (mEq.)		
1	8.4	40.1	23.0
2	21.5	22.1	20.0
3	25.1	21.8	...
4	28.5	53.5	15.2
Average	20.8	34.4	19.4
5 (Control)	22.3	21.2	20.1
	Potassium (mEq.)		
1	12.0	36.0	33.9
2	19.1	18.0	20.5
3	33.7	29.6	...
4	27.8	39.7	30.7
Average	23.1	30.8	28.4
5 (Control)	23.7	16.9	25.8
	Na/K Ratio		
1	0.05	0.8	0.2
2	0.5	1.5	0.4
3	0.03	0.1	...
4	0.04	0.8	0.03
Average	0.15	0.8	0.21
5 (Control)	0.03	1.0	0.3
	Urine (ml.)		
1	300	1464	800
2	495	528	496
3	733	660	...
4	757	893	300
Average	571	886	532
5 (Control)	420	480	495

TABLE III

Relative Increase in Electrolyte and Water Excretion Following Progesterone Therapy

	Patients with Congestive Heart Failure (× normal excretion)	Control Case (× normal excretion)
Sodium	6.5	2.0
Chloride	1.6	0.0
Potassium	1.3	0.7
Na/K ratio	5.3	3.0
Water	1.5	0.0

mEq./day in the other period); and (2) the behavior of metabolic changes during administration of progesterone plus hydrochlorothiazide, and during administration of hydrochlorothiazide alone in the different periods of sodium intake (Tables VII and IX.) The increase of metabolic changes induced by progesterone in both periods of different sodium intake in this case was definitely different (Table X.) As for the weight, there was a gain of 2.4 kg. and a loss of 4.3 kg., respectively, in both periods.

As to the data in Table IX, there are two periods that can be properly compared, for the sodium intake was low in both. When related to changes induced by hydrochlorothiazide alone, the increase of metabolic changes caused by associating progesterone with hydrochlorothiazide are as follows:

	Increase × Normal
Sodium	2.3
Chloride	4.0
Potassium	0.9
Na/K ratio	2.3
Water	2.03
Weight	3.8

There was not much difference between the period of hydrochlorothiazide administration alone with high and low sodium intake (Table IX.) The data obtained in both periods are similar, except for the chloride excretion which was much higher in the period with high sodium intake than in the period with low intake.

COMMENTS

Clinical conditions accompanied by severe edema in which a high urinary excretion of

TABLE IV
Water and Electrolyte Balance in Case 1 (Congestive Failure)

Days	Water (ml.)	Sodium (mEq.)	Potassium (mEq.)	Chloride (mEq.)	Na/K Ratio	Weight (kg.)	Progesterone Dose (mg.)
1	+110.0	−0.68	−11.0	−5.0	0.06	76.4	...
2	+340.0	+0.01	+13.1	−1.1	0.05	76.4	...
3	−85.0	−0.2	+11.4	−31.0	0.06	76.6	50
4	−490.0	−0.8	+11.9	−17.5	0.08	76.4	50
5	0.0	...	...	...	...	75.6	50
6	−430.0	−2.7	+7.4	−16.1	0.14	75.4	50
7	−160.0	−3.5	+8.1	−9.9	0.1	75.150	100
8	−1080.0	−34.7	+1.4	−32.2	1.1	75.3	100
9	−1850.0	−54.0	+1.4	−64.2	1.7	74.6	100
10	−1280.0	−47.1	−12.6	−46.0	1.0	73.9	100
11	−700.0	−33.4	−10.3	−32.6	0.8	72.5	100
12	+380.0	−10.2	+6.5	−13.0	0.4	72.2	100
13	−1200.0	−27.4	−17.8	−44.6	0.5	72.8	100
14	−380.0	−3.0	−0.5	−18.9	0.3	72.5	...
15	−20.0	+3.3	+12.9	−15.5	0.2	72.5	...
16	−200.0	−2.8	+7.7	−13.2	0.4	72.0	...
17	+335.0	+9.2	+20.6	+3.2	0.1	72.4	...
18	−100.0	+8.8	−1.9	−9.0	0.06	73.4	...
19	−200.0	+8.35	+3.5	−13.5	0.05	73.3	...
20	−480.0	+9.95	+9.4	−12.8	0.05	74.1	...
21	+100.0	+8.1	+22.4	−3.9	0.2	74.4	200
22						75.6	

+ = Positive balance. − = Negative balance.

aldosterone was found, such as cirrhosis of the liver, nephrosis and congestive heart failure, were called "secondary hyperaldosteronism" by Conn. However, one can always find an inverse relationship between aldosterone excretion and natruresis in cases of congestive heart failure.[6] There seems to be no doubt that the chief factor in the regulation of the aldosterone secretion in normal subjects is the fluid volume.[7–11] Therefore, there is an apparent contradiction in the explanation of the hyperaldosteronism in cases of congestive heart failure.

There is, however, an outstanding difference in the behavior of aldosterone and sodium excretion in cases of primary and secondary hyperaldosteronism. Therefore, it is possible that the edema of congestive heart failure appears earlier than the hyperaldosteronism.[7,8] In other words, the hypersecretion of aldosterone in such cases is most probably caused by changes of plasma osmolarity which are brought about by an increase in water retention; this in turn is greater than the sodium reabsorption induced by the decreased glomerular filtration rate, thus establishing an extracellular hypotonic syndrome.[10,11] Subsequently, there is a stimulation of the diencephalic centers and

TABLE V
Total Urinary Losses in Case 6 (Cirrhosis of Liver)

Period	Sodium (mEq.)	Chloride (mEq.)	Potassium (mEq.)	Urine (ml.)	Weight (kg.)
1st	10.9	126.6	89.7	2,450.0	
2nd	806.6	1,073.1	519.3	15,370.0	+4.3
3rd	113.7	334.7	297.0	6,210.0	

TABLE VI
Daily Average of Urinary Losses in Case 6

	1st Period	2nd Period	3rd Period
Sodium (mEq.)	1.4	50.4 (36 times)	16.2
Chloride (mEq.).	18.1	67.0 (3.7 times)	47.8
Potassium (mEq.).	11.2	32.4 (2.8 times)	42.4
Na/K ratio...	0.13	1.5 (11.5 times)	0.4
Urine (ml.)..	308.2	960. 6 (3.1 times)	887.1

TABLE VII
Daily Water and Electrolyte Balance in Case 6

Days	Water (ml.)	Sodium (mEq.)	Potassium (mEq.)	Chloride (mEq.)	Ratio Na/K	Weight (kg.)	Treatment	
							Progesterone (mg.)	Hydrochlorothiazide (mg).
1	+1,170.0	+72.6	+95.85	+98.3	0.1	72.5	...	...
2	+810.0	+106.4	+97.5	+95.2	0.2	72.2	...	...
3	+270.0	+108.5	+100.5	+73.8	0.3	71.6	...	...
4	+540.0	+108.0	+91.9	...	0.1	72.0	...	...
5	+740.0	+109.3	+97.1	+86.1	0.1	73.0	...	...
6	+660.0	+92.7	+65.6	+76.0	0.1	73.1	...	...
7	+900.0	+109.7	+74.0	+69.8	0.08	73.8	...	...
8	+650.0	+103.2	+71.8	+78.4	0.06	74.9	...	...
9	+270.0	+102.6	+87.8	+77.9	0.3	75.4	100	...
10	+950.0	+83.2	+101.4	+74.5	1.3	75.5	100	...
11	−100.0	+89.7	+69.8	+15.5	0.5	76.0	100	...
12	+650.0	+105.5	+85.7	+80.2	0.2	76.6	100	...
13	+350.0	+43.9	+78.0	+38.7	0.9	76.8	200	...
14	+300.0	+36.7	+62.7	+12.3	1.0	77.4	200	...
15	+150.0	+33.2	+66.5	−17.5	1.4	77.4	200	...
16	+150.0	+31.4	+97.5	−19.0	1.6	77.4	200	...
17	−250.0	−42.3	+58.8	−41.4	2.2	77.8	200	...
18	−470.0	−48.8	+50.1	−61.0	1.9	77.4	200	...
19	−445.0	−88.0	+44.7	−83.7	2.6	77.0	200	...
20	−100.0	−80.4	+50.5	−78.6	2.8	76.3	200	...
21	−585.0	−74.1	+45.5	−76.2	2.3	76.0	200	...
22	−300.0	−28.0	+43.9	−40.5	1.0	74.7	200	...
23	−590.0	−100.1	+25.3	−73.1	1.9	74.4	200	...
24	−600.0	−92.1	+35.3	−67.0	2.2	73.5	200	...
25	−2,620.0	−269.1	+13.2	−318.9	5.5	73.0	200	200
26	−3,950.0	−507.1	−32.3	−440.1	4.5	70.3	200	200
27	−2,775.0	−326.0	+4.1	−308.8	4.3	66.5	200	200
28	−350.0	−115.5	+6.7	−236.2	2.9	62.7	200	...
29	−1,025.0	−126.0	+21.3	−100.0	2.2	...	200	...
30	−440.0	−40.9	+23.5	−42.1	0.8	61.3	...	...
31	−275.0	−16.0	+30.5	−11.3	0.5	61.2	...	...
32	+150.0	+0.2	+27.8	−4.9	0.1	60.8	...	...
33	+950.0	+2.6	+28.5	−8.7	0.1	61.0	...	...
34	−75.0	+73.8	+54.0	+51.3	0.1	61.5	...	...
35	+275.0	+75.0	+80.8	−33.2	0.2	61.6	...	...
36	+290.0	+67.4	+90.3	−18.7	1.0	61.8	...	...
37	−1,150.0	−141.4	+10.8	−416.0	2.4	62.3	...	200
38	−490.0	+13.6	+22.8	−211.5	0.8	60.8	...	...
39	+300.0	+28.7	+30.0	−14.7	0.1	60.4	...	...
40	+100.0	+0.6	+26.6	−16.4	0.2	60.8	...	...
41	+105.0	...	...	...	...	61.1	...	...
42	−960.0	−170.0	+22.0	−79.7	2.1	61.3	...	200
43	−50.0	−30.0	−4.4	−72.1	0.5	60.4	...	...
44	−40.0	−2.3	+31.1	−10.1	0.2	60.3	...	...

+ = Positive balance. − = Negative balance.

a liberation of glomerulotropin, with its consequent stimulation of the zona glomerulosa of the adrenal cortex for the secretion of aldosterone.[8,11–13] Thus, one should not consider the secretion of aldosterone as the primary factor but rather as an attempt to preserve the homeostasis of the body, causing a vicious cycle in the production of edema.

By means of synthetic steroids (SC 5233 and SC 8109)[14,15] it has been possible to induce a significant natruresis, which is most probably brought about by a competitive action in the

TABLE VIII
Difference in Water and Electrolyte Excretion with Different Sodium Intake (Case 6)

	Before Progesterone Therapy		During Progesterone Therapy			
	High Na Intake	Average	High Na Intake	Average	Low Na Intake	Average
Diuresis (ml.)	2,450	308	5,350	658	10,020	1,252
Sodium (mEq.)	10.9	1.4	212.1	26.5	594.5	74.3
Chloride (mEq.)	126.6	18.1	426.4	53.3	646.7	80.0
Potassium (mEq.)	89.7	11.2	214.6	26.8	304.7	38.1
Na/K ratio	...	0.13	...	0.9	...	2.1
Weight (kg.)	+2.9	...	+2.4	...	−4.3	...

TABLE IX
Effect of Hydrochlorothiazide with Different Sodium Intake (Case 6)

	Progesterone (200 mg.) plus Hydrochlorothiazide (200 mg.)		Hydrochlorothiazide (200 mg.)			
	25th, 26th and 27th Days, Low Na Intake	Average	37th Day, High Na Intake	Average	42nd Day, Low Na Intake	Average
Diuresis (ml.)	11,000	3,667	2,000	2,000	1,800	1,800
Sodium (mEq.)	1,233	411	220	220	180	180
Chloride (mEq.)	1,111	370	486	486	91	91
Potassium (mEq.)	263	88	90	90	90	90
Na/K ratio	...	4.8	...	2.4	...	2.1
Weight (kg.)	−10.3	−3.4	−1.5	−1.5	−0.9	−0.9

renal tubule with aldosterone, as shown by Liddle[15] in seven patients with congestive heart failure.

Landau et al.[1–5] admit that the metabolic change produced by progesterone is due to its blocking effect of the peripheral action of aldosterone. It is possible that it acts on the enzymatic system of the kidney, which is responsible for the sodium reabsorption under the hormonal influence of aldosterone. If one takes as an index of aldosterone-like adrenocortical activity the Na/K ratio, as do several investigators,[14,16–19] our results corroborate the point of view of Landau et al.

As to diuresis, it seems that the patient in Case 1 behaved differently from the other three (Tables I and II.) In the last three, the increase of water diuresis caused by progesterone was proportionally smaller than that of sodium diuresis. The opposite occurred in Case 1 in which the increase of water excretion was proportional to natruresis. In this patient, contrary to the other three, the diet contained only 1 mEq. of sodium long before the administration of progesterone. The same happened to the patient with atrophic cirrhosis of the liver (Case 6). The diuresis increased 2.2 and 4.1 times, respectively, with high and low sodium

TABLE X
Increase in Water and Electrolyte Excretion Produced by Progesterone Therapy with Different Sodium Intake

	Sodium Intake	
	More than 80 mEq./Day (× normal excretion)	11.6 mEq./Day (× normal excretion)
Sodium	18.9	53
Chloride	2.9	4.4
Potassium	2.3	3.3
Na/K ratio	6.9	16.1
Water	2.1	4.1

intake, while the natruresis increased 18.9 and 53 times, respectively.

It is interesting to compare the averages for natruresis obtained by Summerskill and Crabbe[20] in two patients with cirrhosis of the liver with amphenone B and the data we obtained using progesterone. Those authors obtained for both patients an average of 31.43 mEq. of sodium excretion per day while we obtained the average of 50.4 mEq. per day.

Finally, the striking natruresis obtained by the administration of progesterone plus hydrochlorothiazide, when compared to the natruresis obtained by progesterone and hydrochlorothiazide alone, should be pointed out.

Summary

1. In adequate dosage progesterone caused striking changes of the water and electrolyte balance in four patients with congestive heart failure and one with cirrhosis of the liver.

2. Progesterone caused an increased excretion of sodium which was much greater than that of water, chloride and potassium.

3. The excretion of sodium induced by progesterone was not necessarily proportional to that of water.

4. These results confirm the current belief that progesterone acts by antagonizing the action of aldosterone on water and salt reabsorption in the renal tubules.

5. Considering that progesterone caused a greater loss of urinary sodium and a smaller loss of urinary water, one feels justified in thinking that other hormonal influences are involved in the pathogenesis of the edema in these cases.

Acknowledgment

We wish to express our appreciation for the valuable help of Miss Iracema Meira Villasboas in the performance of most of the urinary electrolyte determinations.

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The Electrocardiogram in Thyrotoxicosis*

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ALTHOUGH extensive literature is devoted to the electrocardiographic effects of thyrotoxicosis, there is relatively little meaningful information available to assist the clinician in the diagnosis and care of the thyrocardiac patient. A wide variety of nonspecific effects have been reported but there is general disagreement as to their incidence and relation to the thyrotoxic state. These include sinus tachycardia, atrial fibrillation, prolonged atrioventricular conduction, increased duration and amplitude of the P waves, left ventricular hypertrophy and nondiagnostic T wave changes.[1-7] White[1] states that thyrotoxicosis is rarely accompanied by abnormalities in the electrocardiogram other than sinus tachycardia or atrial fibrillation. He briefly alludes to inverted T waves in rare cases of hyperthyroidism and suggests that a sympathetic nervous effect may be the provocative factor. In his textbook Friedberg[5] concurs with White's general position and states: "Occasionally I have observed abnormalities of the QRS complexes, the R-ST segments, or the T waves, which, however, could reasonably be attributed to associated myocardial damage caused by coronary disease or the effects of digitalis." Gordon,[6] on the other hand, describes reversible T wave abnormalities in 19 per cent of 121 hyperthyroid patients. Lepeschkin[7] referred to a case reported by Duchosal and Henry.[8] This was a fifty year old thyrotoxic female patient in whom angina occurred. Her electrocardiograms showed S-T segment elevation and T wave inversion. The authors commented on the sudden changes in the electrocardiogram and were perplexed by the lack of correlation between the ST-T changes and bouts of chest pain. At autopsy there was focal myocardial fibrosis but the coronary arteries were normal. Prolongation of the P-R interval has been noted by a number of observers[9,10] and denied by others.[11] It is apparent that although the electrocardiographic manifestations of hyperthyroidism have received considerable attention, a controversy still exists as to their specificity and frequency.

SELECTION OF CASES

During a recent two year period twenty-seven patients seen in the Thyroid Clinic at the Los Angeles County General Hospital had electrocardiograms reported as suggestive of myocarditis or pericarditis. A preliminary review of this group of cases showed many of them to have strikingly similar abnormalities. These abnormalities consisted of a prolonged P-R interval, elevation of the S-T segment with terminal T wave inversion and relative shortening of the Q-T interval. Initially it was decided to review these twenty-seven cases of thyrotoxicosis with abnormal electrocardiograms in an attempt to define and elucidate these changes. The series was expanded to a total of 123 patients when it appeared that a distinctive electrocardiographic pattern had emerged. The latter group was chosen at random from a large series of patients with hyperthyroidism followed carefully in the Thyroid Clinic at the Los Angeles County General Hospital.

All patients were studied on the wards of the Hospital by the house staff and the thyroid service. In every case the diagnosis of hyperthyroidism was confirmed by clinical evidence as well as by an elevated protein-bound iodine in the serum and an elevated uptake of radioactive iodine.

Those patients manifesting signs, symptoms or laboratory features of complicating disorders such as hypertension, coronary artery disease or syphilis were not included in the series. A particular effort was made to eliminate diseases such as rheumatic fever and disseminated lupus erythematosus. Since the tracings on many of the patients in this study were reported as compatible with myocarditis or pericarditis, laboratory studies were obtained to rule out coexisting disorders. If the patient manifested any signs or symptoms of the rheumatic state such as polyarthritis, chorea, significant murmurs, etc., he was eliminated from this study. Any patient receiving digitalis or other drugs known to affect repolarization was also excluded.

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TABLE I
Age and Sex Distribution in 123 Patients with Thyrotoxicosis

Age Group (yr.)	Male	Female
10–20	1	1
20–30	4	20
30–40	3	16
40–50	6	18
50–60	8	20
Over 60	2	24
Totals	24	99

S-T and T Changes: The most striking change was the presence of generalized ST-T abnormalities noted in 22.7 per cent of all cases. These ST-T abnormalities were of similar nature and distribution. They consisted of elevation and coving of the S-T segment associated with terminal T wave inversion. The S-T segment usually arose at or 1 to 2 mm. above the isoelectric line, ascended in a gentle curve with its convexity directed superiorly and then became coved to form the inverted T wave. Depression of the S-T segment was not observed. T wave inversion was more frequently of the asymmetrical type.

TABLE II
Summary of Electrocardiographic Changes

Age Group (yr.)	Patients (no.)	Atrial Fibrillation	ST-T Changes	P-R Prolongation	Q-T Short	Sinus Tachycardia
10–20	2	0	0	1	0	1
20–30	24	0	13	5	7	17
30–40	19	1	4	1	4	10
40–50	24	3	3	1	1	5
50–60	28	7	5	0	4	4
Over 60	26	4	3	3	2	9
Totals	123	15	28	11	18	46

Serial electrocardiograms were obtained in the majority of cases employing the three standard limb leads, the three augmented unipolar limb leads and chest leads V_1 through V_6.

The tracings on each patient were carefully analyzed for the following features: (1) rate—atrial and ventricular; (2) rhythm; (3) P-R interval; (4) Q-Tc interval (corrected for the heart rate using Bazett's formula)[12]*; (5) S-T segment variations; (6) T wave changes.

Since our initial survey indicated a significant incidence of ST-T abnormalities, in addition to Q-Tc and P-R interval changes, our study was mainly confined to these. The percentage of hyperthyroid patients with P wave abnormalities, QRS changes and left ventricular hypertrophy has been dealt with extensively, albeit controversially, in the literature.[13,14]

RESULTS

The results of the analysis are shown in Tables I and II.

* Bazett's formula: Q-T corrected = $\frac{\text{Q-T interval in seconds}}{\sqrt{\text{Cardiac cycle in seconds}}}$. The corrected Q-T will be referred to as the Q-Tc.

The predominance of these ST-T changes in females between the ages of twenty to thirty years is most interesting and deserves further investigation.

The ST-T abnormalities, when present, were generally distributed over the entire precordium in addition to the bipolar and unipolar limb leads, depending on heart position. In the vertical, semivertical and intermediate heart positions, leads II, III and aVF most frequently reflected these changes. Leads I, II and aVL were more often involved in the horizontal and semi-horizontal positions. Frequently, the ST-T abnormalities were noted in all bipolar and unipolar leads irrespective of heart position. A notable feature of the tracings with ST-T changes was the evanescent nature of these abnormalities (Figs. 2 and 3). On occasion, they would be present one day and absent the next with no obvious change in the patient's clinical picture.

Q-T Interval: A shortened Q-Tc interval was found in eighteen or 17 per cent of the

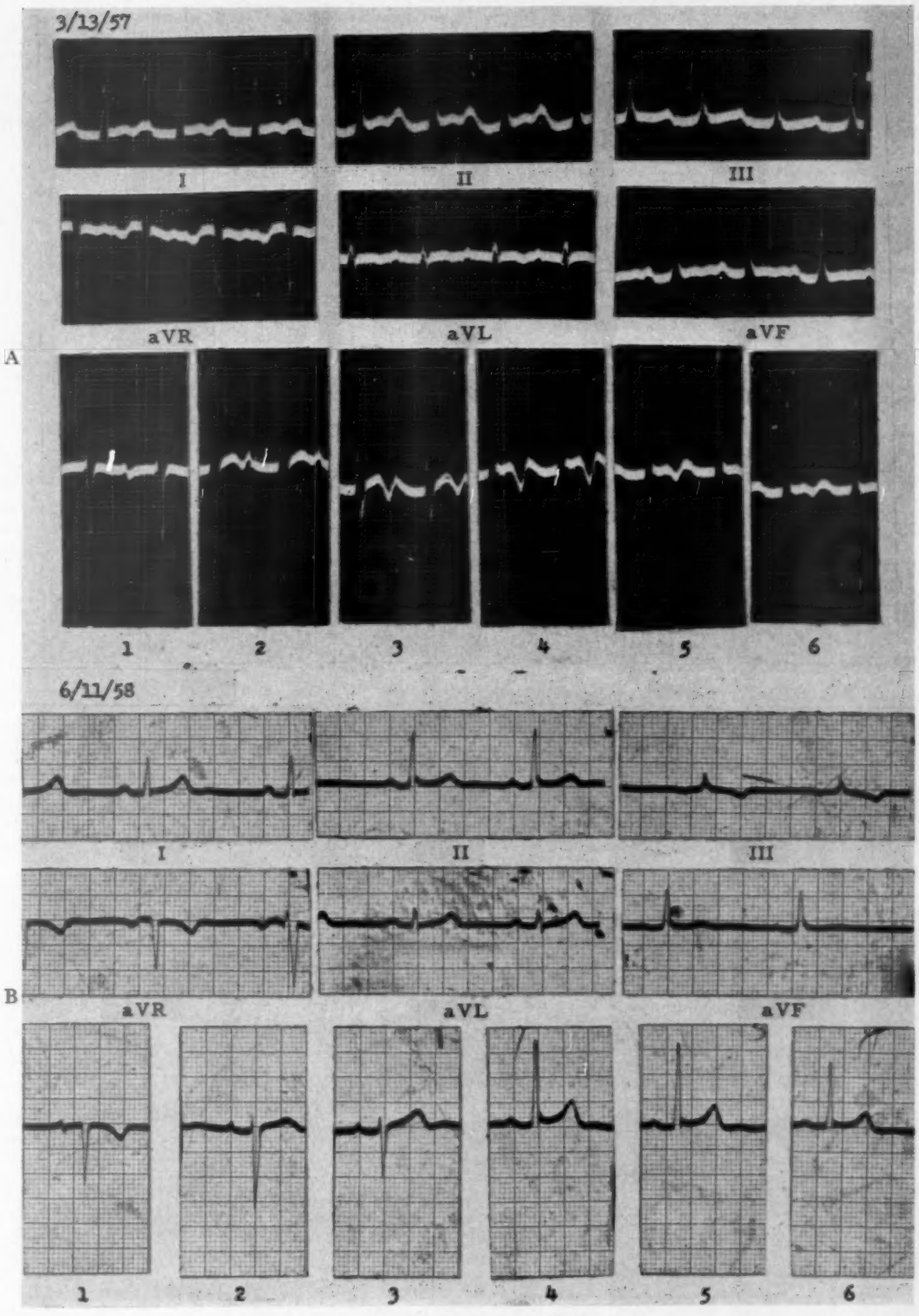

FIG. 1. Case 1. Electrocardiograms (A) during and (B) after treatment of hyperthyroidism.

total series, omitting those patients who had received digitalis. Significantly, thirteen of the twenty-eight patients with ST-T changes presented a shortened Q-Tc interval. Of the remaining fifteen patients with ST-T changes, twelve had normal Q-Tc intervals and three manifested slight prolongation of the Q-Tc. A significant number of thyrocardiac patients, twenty or 16.2 per cent, with no electrocardiographic abnormalities other than sinus tachy-

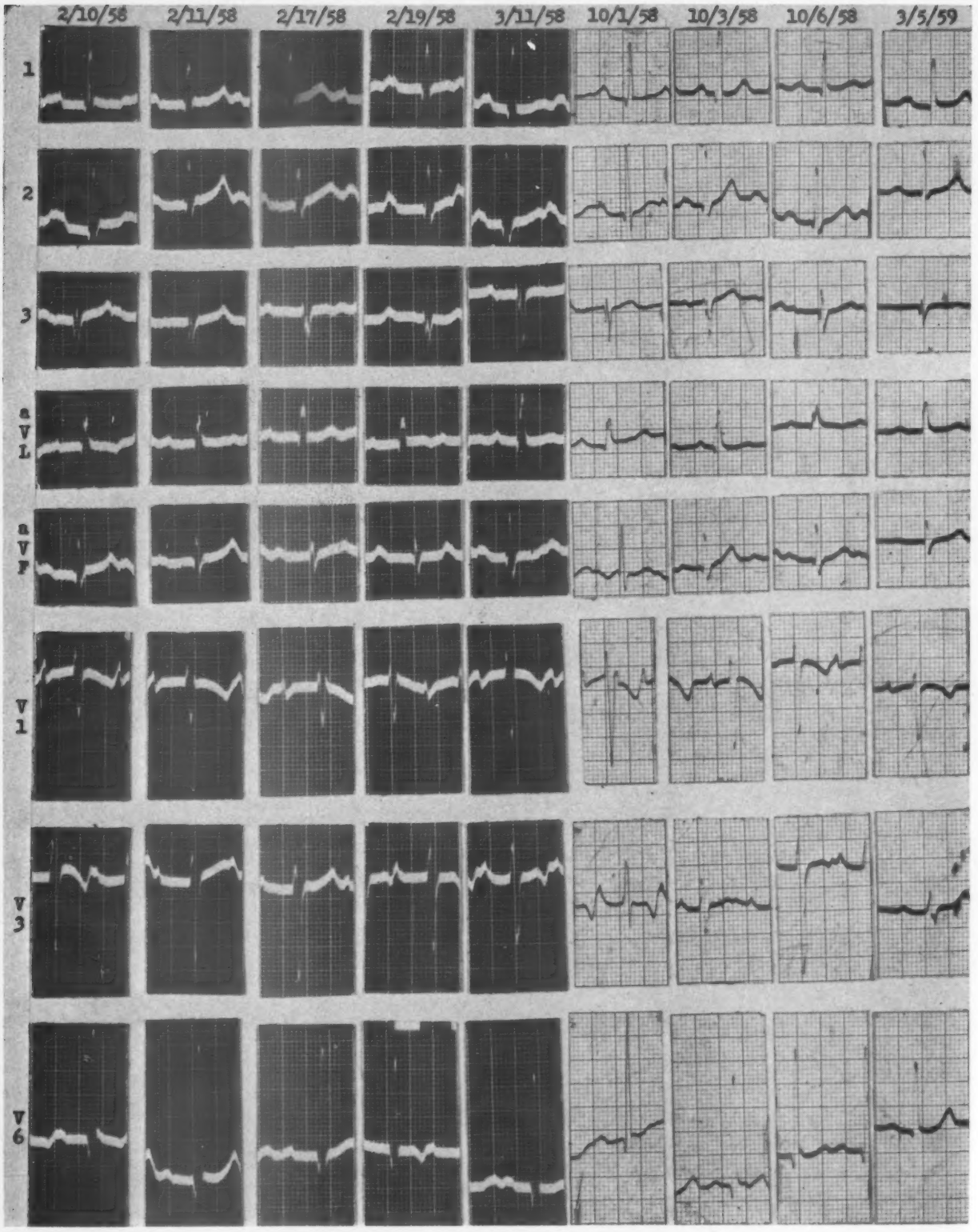

FIG. 2. Case 2. Serial electrocardiograms.

cardia revealed shortening of the Q-Tc interval.

P-R Interval: The P-R interval was prolonged in 8.9 per cent of the entire series and in 21 per cent of those with ST-T abnormalities. Prolongation, notching and slurring of the P wave was frequently observed in those patients with abnormally long P-R intervals. In one instance (Fig. 2) the P-R interval measured

0.36 second. In contradistinction to the fleeting nature of the ST-T changes, prolongation of the P-R interval tended to persist and was often apparent after the patient had become euthyroid.

Illustrative Cases

Case 1. This was a twenty-four year old Negro woman with a history of tiredness, ten pound weight loss despite a good appetite, prominent eyes and palpitations. These symptoms and a diffusely enlarged thyroid gland suggested hyperthyroidism. The PBI was 15.7 μg. The uptake of radioactive iodine was 52 per cent in four hours and 70 per cent in twenty-four hours. Chest roentgenogram was normal. On March 5, 1957, she received 5 mc. of radioactive iodine which was sufficient to alleviate hyperthyroidism. The PBI subsequent to treatment has been 6.2 or 6.3 μg. on several occasions.

Electrocardiographic Findings (*Fig. 1*): Prior to treatment (Fig. 1A) a sinus tachycardia of 104 per minute is present. The P waves are grossly notched and widened to 0.14 second and the P wave axis is deviated slightly to the left. The P-R interval is prolonged and measures 0.32 second. Slight elevation of the S-T segment with coving and asymmetrical T wave inversion is noted in leads I, II, aVF, and V_2 through V_6. The normal Q-Tc interval for this heart rate is 0.25 second whereas the calculated Q-Tc is 0.23 second which is 8 per cent below the normal value.

Serial tracings taken during the two month period following radioactive iodine treatment revealed no essential changes. The tracing taken fifteen months later (Fig. 1B) when the patient had recovered shows the heart rate to be 55 per minute and regular. No ST-T abnormalities are noted. T_3 is inverted but this is a normal variant since T in aVF is of smaller amplitude than in aVL. P waves are of normal width and the P-R interval is within normal limits for this rate. The Q-Tc interval has also returned to normal.

Case 2. This was a twenty-six year old Negro woman who had classical symptoms and signs of hyperthyroidism. She had a diffusely enlarged 80 gm. goiter, hepatomegaly and anemia. Aside from a prolonged prothrombin time, liver function studies were normal. The PBI was 12.6 μg. The uptake of radioactive iodine was 85 per cent in twenty-four hours. The patient was given propylthiouracil and became euthyroid before treatment with 7 mc. of radioactive iodine on June 27, 1958. However, there was a recurrence of hyperthyroidism which required additional treatment with 7 mc. of radioactive iodine on October 3, 1958. The PBI was 18.5 μg. and the I^{131} uptake was 86 per cent in twenty-four hours prior to the second administration of radioactive iodine. She is now euthyroid. Her PBI was 6.3 μg. on January 7, 1959.

Electrocardiographic Findings (*Fig. 2*): On February 19, 1958, the atrial and ventricular rate is 95 per minute. The P waves arise at the termination of the T waves, measure 0.14 second in width and are grossly notched. The P-R interval is 0.28 second. Diaphragmatic infarction is suggested by the prominent Q in II, III and aVF, but the ST-T changes do not support the diagnosis of recent inferior infarction. Instead, they suggest ischemia and a widespread injury current involving the anterior surface of the heart. The Q-Tc interval is 0.26 second which is within normal limits. The diagnosis of left ventricular hypertrophy is suggested by the high voltage over the precordium.[15]

The tracing on February 11, 1958 reveals a dramatic shift of the T wave vector. T waves are now upright and peaked over the precordium. P-R prolongation of 0.28 second and abnormal P waves persist. The Q-Tc interval has lengthened somewhat but is still within normal limits.

On February 17 the only change that has occurred in the six day period between these two tracings is that the T waves are no longer peaked.

On February 19 generalized T wave abnormalities have again appeared in a period of twenty-four hours. The T waves are not as deeply inverted as they were initially and the Q-Tc interval is again normal. The P-R interval is increased to 0.32 second and the morphology of the P waves is unchanged.

The tracing on March 11, 1958 taken following initial treatment shows some improvement in the appearance of the T waves in leads I, aVL and V_6. The P-R interval has decreased to 0.24 second and the ventricular rate is relatively unchanged. A normal Q-Tc interval is again observed.

Following recurrence of hyperthyroidism seven months later (October 1), primary T wave abnormalities are again seen but are less pronounced. Terminal inversion of the T wave is again noted in V_3 whereas the T is flattened in leads I, aVL and V_6. Delayed A-V conduction persists but is now only 0.22 second. The Q-Tc interval is normal.

The record on October 3 has again reverted to normal within a two day period. The P-R interval is also normal. Notched P waves, however, are still noted.

On October 6, T wave changes have recurred along with lengthening of the P-R interval to 0.24 second. The Q-Tc interval is normal.

With reversion to the euthyroid state (March 5, 1959) all ST-T changes have once again reverted to normal. The P-R interval (0.24 second) is slightly prolonged for this heart rate.

Case 3. The patient is a twenty-three year old Negro woman who underwent thyroidectomy in 1954 because of toxic goiter with exophthalmos. On September 11, 1957, she was given 7 mc. of radioactive iodine as treatment for recurrent hyperthyroidism. On October 11, 1957, she entered the hospital in diabetic ketoacidosis and had evidence of thyrotoxicity for which she was given methima-

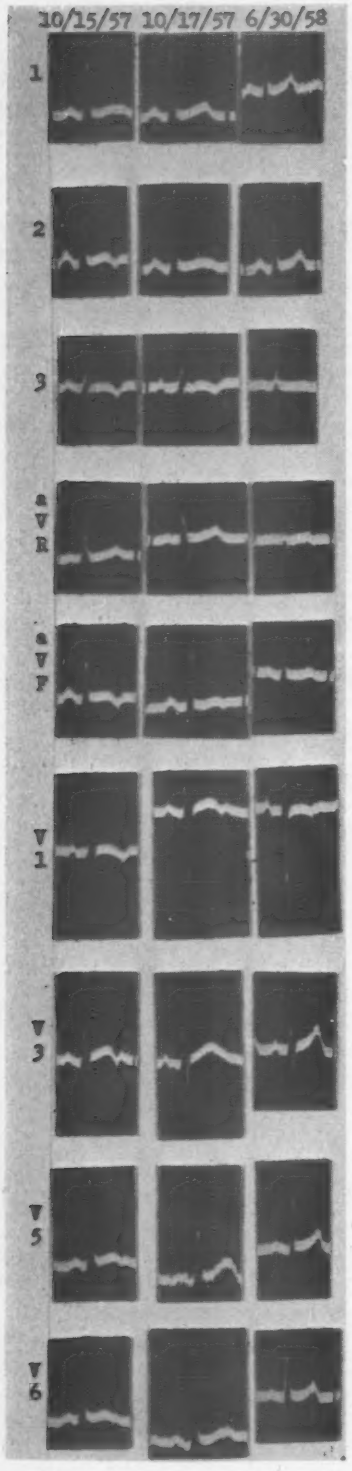

FIG. 3. Case 3. Serial electrocardiograms.

zole (Tapazole®). The patient responded to this therapy but symptoms and signs of thyroid toxicity appeared when it was discontinued. The PBI was 9.7 μg. and the twenty-four hour uptake of radioactive iodine was 58 per cent on April 1, 1958, when additional treatment with 7 mc. of radioactive iodine was given. After a period of transient hypothyroidism, the patient became and remained euthyroid. In June, 1958, she entered the hospital again because of diabetic ketoacidosis. The PBI was 4.7 μg.

Electrocardiographic Findings (*Fig. 3*): On October 15, 1957, the rhythm is a sinus tachycardia at a rate of 104 per minute. There are no abnormal P or QRS changes and the P-R interval is within normal limits. The S-T segment is coved and the T wave inverted in leads II, III and aVF. Gradual ascent of the S-T segment associated with terminal T wave inversion is noted in all precordial leads. The Q-Tc interval is 0.23 second which is 8 per cent below normal.

The atrial and ventricular rate on October 17 is 90 per minute. Dramatic T wave changes have occurred in the two days since the preceding tracing. The T waves are now distinctly upright in leads I and II, inverted in III and flattened in aVF. Slight S-T segment elevation with upright T waves characterize the precordial leads. Despite the notable shift of the T wave vector to a more normal anterior direction this tracing is still considered abnormal in the presence of the flattened T in aVF and resultant inverted T in lead III. The Q-Tc interval has increased to 0.28 second which is within the normal range.

A sinus tachycardia is again noted on June 30, 1958 at 120 per minute. The tracing is otherwise normal. T waves are now upright in leads III and aVF. The Q-Tc interval is 0.21 second and is normal for this heart rate.

CASE 4. A forty-nine year old Negro woman entered the hospital in November, 1953 with complaints of nervousness, weakness, weight loss despite a good appetite, polyuria and polydipsia. No goiter was palpable. The chest roentgenogram was normal. The PBI was 13.7 μg. and the uptake of radioactive iodine was 92 per cent in twenty-four hours.

On December 14, 1953, the patient was treated with 7 mc. of radioactive iodine. In August, 1954, she was myxedematous. The PBI was 1.6 μg. and the uptake of radioactive iodine was 6 per cent in twenty-four hours. She did not improve after administration of thyrotropin. Four basal metabolism determinations ranged between −30 and −40. She was treated with triiodothyronine and responded well by December 1, 1954, at which time the basal metabolism was −8. At present she is euthyroid on a maintenance dose of thyroid extract.

Electrocardiographic Findings (*Fig. 4*): The atrial and ventricular rate is 83 per minute on November 19, 1953. There are no P wave or P-R abnormalities. The T wave is normal in all the limb leads except aVL where it is inverted. The S-T segment gradually ascends and terminates in an asymmetrically inverted T wave in V_3. (This was seen also in V_2 and V_4.) T waves are upright in V_5 and V_6. The Q-Tc interval of 0.32 second is within normal limits.

On August 4, 1954 nine months have elapsed since the first tracing and the patient is myxedematous.

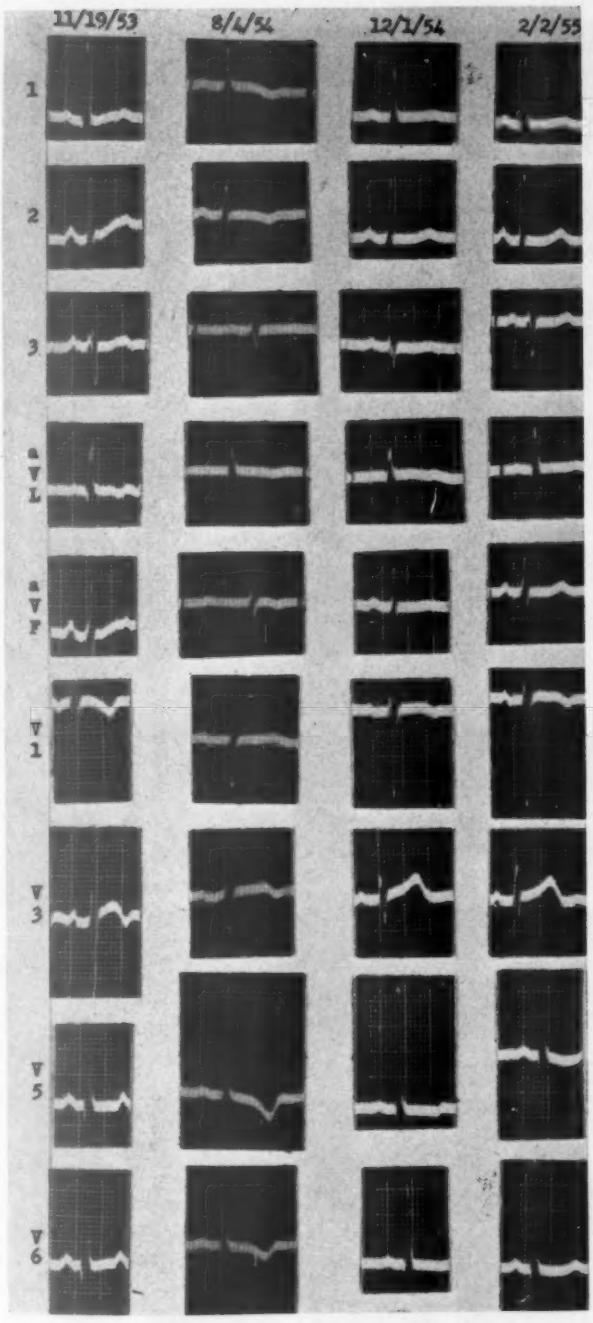

FIG. 4. Case 4. Serial electrocardiograms.

The rate is now 54 per minute. T wave inversion is seen in leads I, II, aVL and aVF. The S-T segment is isoelectric over the precordium and there is symmetrical T wave inversion in V_5 and V_6. The Q-Tc interval is 0.52 second, 17 per cent greater than normal.

On December 1, the patient is euthyroid. The T waves have become upright but of low amplitude in all the bipolar leads and in aVF. A flattened T wave remains in aVL. The T wave is diphasic in V_5 and V_6. The Q-Tc interval is relatively unchanged at plus 10 per cent of normal (0.40 second).

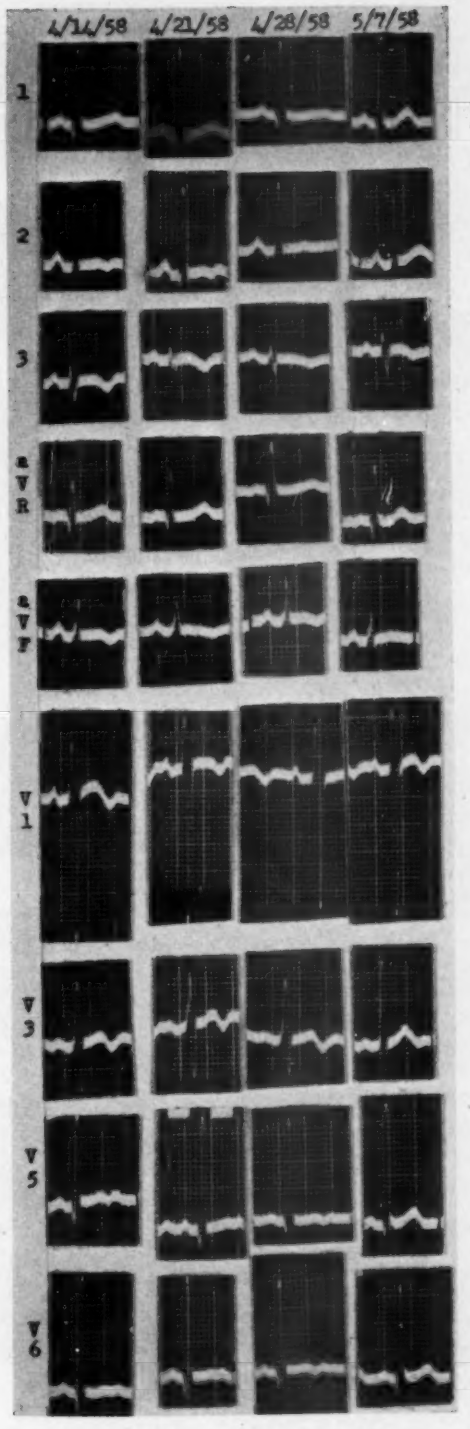

FIG. 5. Case 5. Serial electrocardiograms.

T wave abnormalities are no longer observed on February 2, 1955. The only abnormality is the sagging S-T segment in V_5 and V_6.

CASE 5. This case is that of a twenty-nine year old Negro woman who had a history of diarrhea, weight loss, tachycardia and nervousness. There was marked quadriceps weakness as well as generalized muscular atrophy. She had a diffusely enlarged goi-

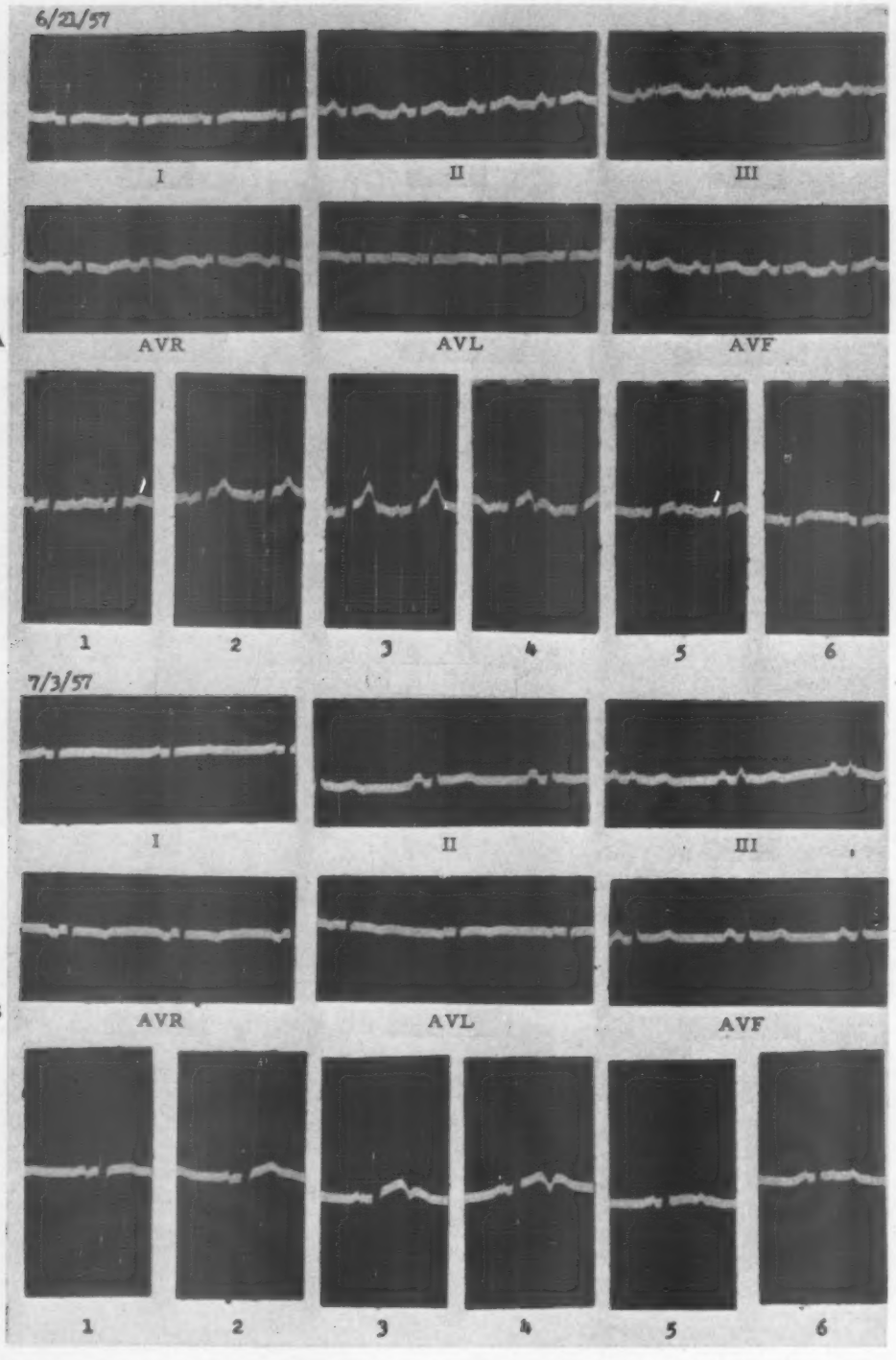

FIG. 6. Case 6. Electrocardiograms during a thyrotoxic crisis (A) and following remission (B) twelve days later.

ter. The PBI was 19 μg. and the uptake of radioactive iodine was 78 per cent in twenty-four hours. The chest roentgenogram was normal. The highest pretreatment hemoglobin was 11.8 gm., the lowest 9.6 gm. By April 28, 1958, the patient had responded to iodothiouracil. A thyroidectomy was subsequently performed.

Electrocardiographic Findings (*Fig. 5*): On April 14, 1958, a sinus tachycardia is identified at a rate of 94 per minute. Symmetrically inverted T waves are noted in leads II, III and aVF. In all precordal leads the S-T segment slopes upward, appears coved and terminates in an inverted T wave. The QRS voltages over the precordium are above normal limits.[9] The Q-Tc interval is 0.26 second which is within normal limits.

The tracing on April 21, 1958 shows relatively little change.

Following treatment the rate has slowed to 82 per minute as of April 28. T wave inversion is less pronounced in leads II, III and aVF. The precordial lead T wave abnormalities are essentially unchanged. The Q-Tc interval has increased to plus 25 per cent of normal and measures 0.50 second.

T wave abnormalities are no longer present on May 7, 1958, and the tracing is now normal. The Q-Tc interval has shortened considerably and is now within normal limits for this heart rate(0.26 second).

CASE 6. This fifty-year old white man entered the hospital in May, 1957 with chief complaints of abdominal pain and diarrhea. The history noted weight loss despite a good appetite, marked heat intolerance and weakness. A small goiter (less than 40 gm.) was detected. There were eye signs and myopathy. The PBI of 18.8 μg. and the uptake of radioactive iodine (57 per cent in twenty-four hours) confirmed the diagnosis of hyperthyroidism.

On May 17, 1957, he was treated with 4 mc. of radioactive iodine. He was discharged from the hospital shortly thereafter but on June 18, 1957, he reentered with fever, tachycardia and profuse perspiration. The chest roentgenogram was normal. Pyuria was noted. He was treated for acute pyelonephritis but was also considered to have a thyrotoxic crisis. During this time he developed marked chemosis and other evidence of severe ophthalmopathy. The subsequent course was one of persistent hyperthyroidism with exophthalmos that required multiple treatment before thyroid ablation resulted.

Electrocardiographic Findings (*Fig. 6*): During severe hyperthyroidism (June 21, 1959) the atrial and ventricular rate is 105 per minute. The T wave is flattened in lead I, inverted in aVL and terminally inverted in V_4 through V_6. Gradual ascent of the S-T segment is seen in V_4 and V_5. The Q-Tc interval is 0.24 second which is slightly shortened.

Following control of the hypothyroidism (July 3, 1957) the rate is 65 per minute and T wave abnormalities have persisted. The Q-Tc interval is calculated at 0.36 second, normal for this heart rate.

COMMENTS

In our entire series of 123 patients with hyperthyroidism, forty-six (37.4 per cent) presented a sinus tachycardia with rates above 100 per minute. This finding, in general, is similar to that in previous reports[16] and is apparently related in a crude fashion to the general increase in basal metabolic rate. Atrial fibrillation was the dominant rhythm in fifteen patients or 12.2 per cent of this series.

Prolongation of the P-R interval was found in eleven of the 123 patients (8.9 per cent). Since this interval varies with age and heart rate, proper allowance was given to these factors in arriving at an accurate appraisal. We have been impressed by the frequency with which persistent delayed A-V conduction is seen in hyperthyroidism and believe it has received less emphasis in the literature than it deserves.

The significant incidence of generalized ST-T abnormalities (22.7 per cent) in this random group of hyperthyroid patients was a surprising finding. The predominance of these changes in young women with hyperthyroidism has already been mentioned. These abnormalities were of a stereotyped nature and called forth a remarkably frequent interpretation of "myocarditis or pericarditis" by numerous independent observers. In general the S-T segment was isoelectric or slightly elevated, appeared coved and the T wave was terminally inverted. The ST-T abnormalities were usually distributed over all the precordial leads and most, if not all, the bipolar and unipolar limb leads. The generalized nature of the changes was the factor responsible for the diagnosis of possible myocarditis or pericarditis.

In a study of a series of fifty patients with thyrotoxicosis, Sandler[11] concluded that no significant T wave changes occurred. However, he stated that T wave inversion appeared "in one or other lead in over 50% of the thyrotoxic patients." He did not distinguish between normal and abnormal T wave changes and, therefore, the conclusion is meaningless despite the fact that over 50 per cent of his controls also had T wave changes. Gordan et al.[6] described abnormal T waves in 19 per cent of 121 patients with hyperthyroidism, which consisted of low amplitude, notching, diphasic appearance and abnormal contour. Only the three standard leads and the precordial lead IVF were used to examine these changes. One of his illustrated cases manifests ST-T abnormalities similar to those found in our series. The percentage of patients with abnormal T waves in Gordan's series tallies closely with those in our study.

An interesting and perhaps specific characteristic of the ST-T change is its transitory nature. In many of our patients florid T wave inversion throughout the tracing would vanish within a period of 24 to 48 hours and subsequently reappear within a few days with no obvious change in the patient's clinical status. Transient T wave abnormalities have been described under many different physiologic situations such as hyperventilation, drink-

ing cold liquids, exercise, acute pain, anxiety and others. However, these physiologic T wave variations are not generalized and the T waves appear flat or only very slightly inverted when compared to those seen in the present series.

To our knowledge, shortening of the Q-T interval in thyrotoxicosis has not been reported heretofore. It is well known that systole shortens appreciably with increasing heart rate. Since the Q-T interval is a function of electrical systole, as the heart rate increases the Q-T interval diminishes proportionately. Calculation of the Q-Tc interval is thus important to eliminate the effect of tachycardia on electrical systole and derive a true value dependent upon primary changes in myocardial physiology. Seventeen per cent of our patients presented a shortened Q-Tc interval. Further breakdown reveals that 46 per cent of the patients with ST-T abnormalities manifested a shortened Q-Tc interval. Since digitalis shortens the Q-Tc interval, those patients receiving this drug at any time during their course were not included in the statistical breakdown.

DIFFERENTIAL DIAGNOSIS

In the electrocardiogram, *acute rheumatic carditis* is frequently characterized by generalized T wave changes which resemble those presented in this report.[1,12] Prolongation of the P-R interval often coexists, thus compounding the similarity. However, in cases of active rheumatic carditis with T wave abnormalities the Q-Tc interval is invariably prolonged to a significant degree.[17] This feature serves to separate those cases of rheumatic carditis from thyrotoxicosis since a shortened Q-Tc interval characterizes the latter. Disseminated lupus erythematosus may also be represented by similar T wave changes in the electrocardiogram as a result of an accompanying pancarditis. In our experience the Q-Tc interval has been prolonged in these instances.

In the subacute stage of *idiopathic pericarditis* the S-T segments may become isoelectric and the T waves inverted. Despite numerous reports in the literature[18–20] describing these changes there is nothing to indicate any significant variation of the Q-Tc interval. *Diphtheria* and *viral disorders* such as poliomyelitis[21] may also present themselves with nonspecific T wave changes associated with normal or prolonged Q-Tc intervals.

Myocardial ischemia must also be considered in the differential diagnosis. Usually the T wave abnormalities in ischemia are more localized to either the anterior or diaphragmatic surface of the heart than those seen in thyrotoxicosis. The Q-Tc interval may again differentiate these two disorders since it is usually prolonged in ischemia.

The evanescent nature of the T wave abnormalities in thyrotoxicosis is rarely seen in the specific types of carditis enumerated above. T wave abnormalities persist unchanged for weeks or months in myocarditis and are more transient in hyperthyroidism. Ischemia, however, may also give rise to short-lived T wave changes.

Besides digitalis, which is by far the most frequent offender, the only other entity known to be responsible for shortening of the Q-Tc interval is *hypercalcemia*. However, inversion of the T waves is not seen in hypercalcemia.

PATHOGENESIS OF ELECTROCARDIOGRAPHIC CHANGES

Asboe-Hansen et al.[22,23] have used special staining technics to show mucopolysaccharide deposits in ocular muscles, retrobulbar connective tissue and biopsy specimens of biceps brachii and quadriceps femoris in all cases of hyperthyroidism with eye signs. This is thought to be due to the effect of thyrotropin or a related pituitary factor. It is attractive to speculate that such infiltrations could occur in cardiac muscle and somehow account for the electrocardiographic changes. However, if this were so, one should expect the changes to persist after treatment of hyperthyroidism, as do ophthalmopathy and pretibial myxedema. Such is not the case.

Adrenal Hormonal Factors: The transitory nature of the electrocardiographic changes suggests a neurohumoral factor as the provocative agent. The common derivation of thyroxin and epinephrine from tyrosine[24] supports an inter-relationship between these hormones and suggests a similar pharmacologic effect. In addition, Rogoff and Cortell[25] have shown an increased rate of liberation of epinephrine from the adrenal glands in hyperthyroidism. McGavack[26] has postulated that thyroid hormone sensitizes the organism to the action of adrenal medullary secretion. That altered myocardial metabolism can occur as a result of increased work in meeting the demands of the hyperthyroid state as well as from a direct

effect of thyroxin on the cardiac muscle has long been known.[27–29] Amine oxidase inhibition by thyroxin[30] may well augment the accumulation of sympathogenic catecholamines which produce tissue injury and call for oxygen consumption in excess of the requirements for cardiac work. Enhanced sympathetic stimulation as a concomitant of hyperthyroidism is, therefore, well documented in the literature.

We have recently seen the electrocardiograms of two patients with pheochromocytomas who presented ST-T changes resembling those described in this report. In both instances the Q-Tc interval was at the lower limit of normal. This observation supports the inter-relationship between thyroid hormone and norepinephrine and the resultant effect on the electrocardiogram.

Neurohumoral Imbalance: Hartwell and associates[31] have shown that adrenergic drugs lower the amplitude of the T waves while cholinergic drugs increase their amplitude. Elek et al.[32] have reported that the adrenergic blocking agent, dihydroergocornine, when given intravenously, may change the T waves from inverted to upright in hyperthyroidism or increase their amplitude when normal T waves are found. Central vagal stimulation or a direct myocardial action is presumed to account for the effects of dihydroergocornine.[33] It is conceivable that, for unknown reasons, the patient with hyperthyroidism may suddenly and at times, temporarily, suppress the enhanced sympathetic discharge usually present and substitute, in its stead, a parasympathetic response. This hypothesis is a reasonable one and would explain the resultant shifts of the T wave vector in the electrocardiogram to a more normal direction. Further light may be shed upon this possible neurohumoral imbalance and the dramatic changes it produces in the electrocardiogram by injecting dihydroergocornine in hyperthyroid patients with ST-T abnormalities and noting the response.

Summary and Conclusions

The electrocardiograms of 123 patients with thyrotoxicosis were studied. A significant incidence of generalized ST-T changes was found in addition to shortening of the Q-Tc interval and prolongation of the P-R interval. Transitory T wave abnormalities were a distinctive feature of the disorder. It is suggested that neurohumoral factors may be the responsible agent.

Acknowledgment

The authors wish to thank Dr. Donald W. Petit, Chief of the Endocrine Section and Dr. Boris Catz, Director of the Thyroid Clinic, for their interest and guidance.

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Electrocardiographic Changes Following the Administration of Thyroid Stimulating Hormone (Thyrotropin)*

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THIS REPORT describes certain electrocardiographic changes which occurred when 25 mg. (10 U.S.P. units) of thyroid stimulating hormone (TSH) was administered intramuscularly daily to each of five men for a period of four or five successive days. Although we are not aware of any reports of electrocardiographic alterations following administration of TSH, there is certainly nothing unusual in the occurrence of changes in the electrocardiogram concurrent with increased thyroidal activity, whether drug induced or associated with disease.[1] However, the time relation of the changes which were observed during TSH administration were unexpected and may provide information on the mechanism of thyroid stimulation of the heart.

METHOD AND RESULTS

The subjects, aged forty-six to ninety-two, were clinically euthyroid. They are described in detail elsewhere.[2] Table I summarizes their cardiac and thyroid status. They were examined before TSH was first administered and daily thereafter. Observations of basal metabolic rate (BMR), serum protein-bound iodine (PBI) and accumulation by the thyroid gland of a tracer dose of radioactive iodide (I^{131}) were made as part of a programmed study.[2] Detailed descriptions of these observations and the methods used are given elsewhere.[2–4] The electrocardiograms were taken as a matter of clinical interest. Table II summarizes the electrocardiographic changes and relates these to time of TSH administration and changes in BMR, PBI and I^{131} uptake. Individual cases are described as follows:

CASE HISTORIES

CASE 1. W. D., forty-six years old, was under domiciliary care. He had inactive pulmonary tuberculosis. A leg had been amputated below the knee twelve years previously, following a freezing exposure and bilateral lumbar sympathectomy. There was no history of cardiac disease. Heart size and blood pressure were normal. An electrocardiogram taken five months previously was normal with heart rate of 76 per minute, except for a broad notched P wave in leads II, III, aVF and V_2 to V_4 (Fig. 1).

After three days of TSH administration, counting the day on which the first dose was given as Day 0 (Fig. 1, TSH 3), there was an irregularity of cardiac rhythm which was revealed to be due to a shifting sinus pacemaker and premature atrial systoles, some of which showed aberrant conduction. The average heart rate was 73 per minute. In addition, QRS was increased in amplitude in lead II, aVR, and V_1 through V_6 and exhibited terminal notching or slurring. T was taller in leads I and V_2. On the following day, on which the fifth and last dose of TSH was given (Fig. 1, TSH 4) the electrocardiogram showed a rate of 89 with less than 1 per cent premature atrial systoles. T was diphasic with a sharp terminal inversion in V_4. A day later the rate reached a peak of 114, premature atrial systoles were more frequent and T wave inversion was more widespread and marked, becoming evident in leads II, III and V_2 through V_6. S-T was depressed in V_5. Two days after discontinuance of the drug, the heart rate was 105 but no premature beats were present of almost 200 recorded beats. S-T remained depressed in V_5. T waves were less negative or were positive. On the next day the basal metabolic rate attained the highest value observed. Five days after withdrawal of TSH the T waves were again normal although the heart rate and basal metabolic

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TABLE I
Cardiac and Thyroid Findings in Five Patients Treated with TSH

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (yr.)	46	51	81	88	92
Prior records (yr.)	13	2	8	4	1
Overt symptoms	None	None	None	Mild exertional dyspnea	None
Thyroid examination	Negative	Negative	Negative	Negative	Negative
Cardiac examination:					
Rate* (beats/min.)	64	74	56	68	64
B.P.* (mm. Hg)	115/74	118/80	163/82	140/67	144/80
Murmurs	None	None	Apical systolic	None	Harsh systolic
Heart size on x-ray film (% oversize)	Normal (0)	Normal (+5)	Enlarged (15)	Equivocal (<15)	Enlarged (<20)
ECG: resting	Broad P	Small QRS in limb leads	LVH pattern; small T in I, V_5 to V_6	P-R 0.24; occasional atrial premature systole	P-R 0.25; depressed S-T, low T in I, V_4 to V_6
exercise		Normal ECG; rapid rate	Response normal		Response normal
Basal metabolic rate (%)	+1	−5	+9	+4	+1
Thyroid I^{131} uptake at 24 hr. (% dose)	45	53	48	43	32
Serum protein-bound iodine (μg./100 cc.)	5.7	5.1	7.1	5.9	5.8

* Mean of five determinations at weekly intervals. Measured under basal conditions of BMR test.

rate were still elevated. The precordial T abnormalities, however, were again noted in a record taken ten days later, and inversion of T was demonstrable three weeks after the discontinuance of TSH in leads taken one interspace above and below the standard positions in the left anterior chest. Premature systoles were variably present to the extent of 8 per cent at four days, 15 per cent at fourteen days but were absent in the record taken three weeks after TSH was discontinued.

Comment: In this case, with a single control record which showed only suggestive atrial abnormality, TSH administration was followed by premature systoles, S-T depression and T wave inversion. Since the premature systoles and T wave inversions were variably present long after the drug was stopped, they may have been present irregularly before the treatment or have been dependent on electrode placement. The single control record is inadequate to exclude this possibility. The electrocardiographic abnormalities were first noted, however, before the increase in heart rate became marked and before the increase in basal metabolic rate was significant.

CASE 2. L. G., fifty-one years of age, presented residual memory and personality defects after recovering from acute meningovascular syphilis eighteen months before the study. He was subject to infrequent major epileptiform seizures, a condition which may have preceded his central nervous system disease. These seizures were controlled by phenobarbital and Dilantin®. The cardiac roentgenographic shadow was within the limits of normal size and was of normal contour. Two control electrocardiograms showed rates of 76 and 90 per minute with small QRS complexes in the limb leads. In the first record QRS and T in the precordial leads were also small. In the second record, however, the precordial deflections were taller. The electrocardiographic response to a two step exercise test was normal except for persistent elevation of heart rate.

In an electrocardiogram taken after four days of TSH administration, the heart rate was 103 per minute and the precordial T waves were intermediate in height between the two control records. T waves in leads V_2 and V_3 decreased on the following day to 2 to 3 mm., still within control limits despite the elevated rate. On this day the fifth and final dose of TSH was given. The peak of basal metabolism response occurred a day later. Five days after withdrawal of TSH, T waves were as tall or slightly taller than in control records, and a final tracing eighteen weeks afterward was similar to the first control.

Comment: In this subject there was no significant change in the electrocardiogram. Variations in precordial QRS and T waves were present in the control record and, despite the tachycardia induced by TSH, the T waves

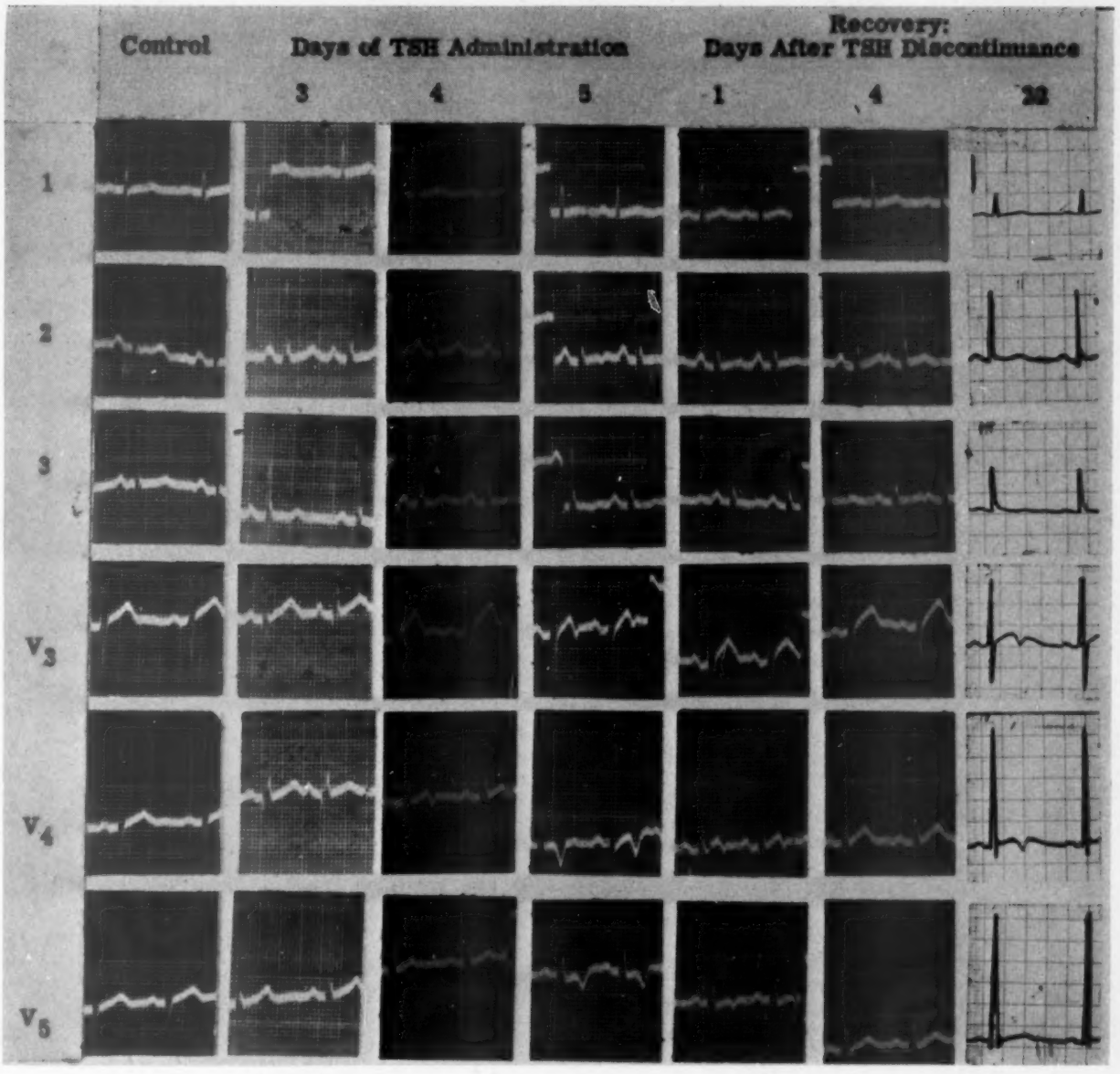

FIG. 1. Case 1. Effect of administration of thyroid stimulating hormone (TSH) on the electrocardiogram. Since the observed abnormalities were demonstrated to a variable degree after the drug was discontinued, they are not definitely ascribable to TSH treatment. A record taken fourteen days after the withdrawal of TSH, described in Table II, is omitted in this figure.

subsequently increased slightly in height in the precordial leads.

CASE 3. A. A., eighty-one years of age, displayed moderate chronic emphysema, systolic hypertension and mild cardiovascular disease presumably consequent to coronary atherosclerosis. He had been known to us for eight years. His cardiac transverse diameter was 15 per cent oversize on roentgenographic examination, compared with mean transverse diameter for his height and weight as given in standard tables. During the seven year period for which electrocardiograms were available, and prior to the first of the two control records taken three years prior to and just before the study, respectively (Fig. 2), there was decrease in T in leads I and V_4 to V_6, decrease in R in I and increase in R in V_2 and V_3. Comparison of the two control records showed no further diminution in T and no change in R.

An electrocardiogram taken after four days of TSH treatment showed a decrease in T in almost all leads, with a striking coving of S-T and an inversion of T in V_4 to V_6. At this time, his heart rate was 73 and symptomatic evidence of increased metabolism was not manifest. Due to the electrocardiographic alterations, however, a programmed fifth dose of TSH was withheld. A day later, however, the heart rate was 85; T was upright in all leads but the S-T

TABLE II

Electrocardiographic Changes Correlated with Changes in Thyroid Function

Case No.	Time Relation of ECG to TSH Administration		Electrocardiogram				Basal Pulse Rate† (per min.)	Basal Metabolic Rate (%)	Thyroid I^{131} Uptake at 24 Hours (%)	Serum Protein-bound Iodine (μg./100 cc.)
	Period	Days*	Heart Rate (per min.)	Premature Systoles (%)	S-T Segment	T Waves				
1	Control		76	0	N‡	N	64§	−2§	45§	5.7§
	TSH	3	73	4	N	Taller in I, V_2	82	+1		
		4	89	<1		Diphasic in V_4, V_5	89	−3	97	16.6
		5	114	9	Depressed in V_5	Inverted in II, III, V_2 to V_6	92	+11		
	Recovery	1	105	0	Depressed in V_5	Diphasic in III, V_4, V_5	80	+27		
		2					102	+36		13.7
		4	88	8	N	Tall in V_3	89	13		10.4
		14	79	15	N	Diphasic in V_4, V_5	81	+17§		
		22				Inverted in V_1, V_3, V_4				
2	Controls		90	0	N	N	74§	−5§	53§	5.1§
			76	0	N	N				
	TSH	4	103	0	N	N	96	+1	74	12.0
		5	109		N	Lower in V_2, V_3	97	+1		
	Recovery	3					103	+18		11.2
		5	99	<1	N	Taller in II, V_3, V_5				
3	Control		68	0	N	Small in I	56§	+4§	48§	7.1§
	TSH	2					64	−1		
		3					70	−5		
		4	73	0	Coved	Smaller, inverted in V_4 to V_6	71	+24	100	16.0
	Recovery	1	85	0	Depressed	N	72	+34		
		21	59	0	N	N	60§	−1§	43§	6.0§
4	Controls		87	4	N	N	68§	+5§	43§	5.9§
			81	0	N	N				
	TSH	2	83	3	N	Lower in V_4, V_5	74	+31		13.2
		3	88	3	Slightly depressed in I, V_5, V_6	Taller in II				
		4	86	6	N	N	79	+13	65	13.3
		5	87	19	N	N				
	Recovery	1	96	20	N	N				11.4
		4					74	+27		10.4
		6	88	10	N	N				

TABLE II (*Continued*)

Case No.	Time Relation of ECG to TSH Administration		Electrocardiogram				Basal Pulse Rate† (per min.)	Basal† Metabolic Rate (%)	Thyroid I^{131} Uptake at 24 Hours (%)	Serum Protein-bound Iodine (μg./100 cc.)
	Period	Days*	Heart Rate (per min.)	Premature Systoles (%)	S-T Segment	T Waves				
5	Controls		71	0	Slightly depressed in I, II, aVL, V_4 to V_6	N	64§	+1§	32§	5.8§
			74	15	Slightly greater depression in V_4 to V_6	Lower in V_3 to V_5				
	TSH	2	77	8	Depressed in I, II, V_4 to V_3	No change	70	+8		11.0
		3	83	18	More depressed in V_4 to V_6	Smaller in V_3, V_4; diphasic in V_5, V_6	76	+16		
		4	82	17	Less depressed in V_4 to V_6	Taller in V_4; upright in V_5	80	+6	92	13.6
	Recovery	1	88	20	Less depressed in V_5, V_6	Upright in V_4, V_5; diphasic in V_6	71	+15		
		2	82	13	Similar to control		77	+16		
		3					82	+58		10.3
		118	72	0	N	As in control	66§	+10§	34§	5.3§

* Counting the first day of administration as Day 0. Thus the day on which the fifth dose of TSH was administered would be designated "TSH 4," the following day as "TSH 5," and successive days thereafter as "Recovery 1," "Recovery 2," etc.

† Calculated on basis of weighted mean data compiled by Shock and Yiengst.[5]

‡ N indicates "normal."

§ Control values were measured during five weeks preceding TSH administration. Values measured during control and long term recovery periods, more precise time relations to days on which TSH was given and electrocardiograms were taken, as well as additional data, are given in Reference 2.

segment was relatively depressed in leads II, III, aVF, V_5 and V_6. On this day the basal metabolic rate reached the highest value observed. Three weeks later the record had returned to control configuration and the electrocardiographic response to standard exercise was normal.

Comment: In this case the administration of TSH was associated with striking changes consisting of coving and depression of the RS-T segment, with diminution and inversion of precordial T in leads V_4 to V_6. These changes occurred prior to maximum observed change in basal metabolism, and were not evoked by an exercise test after therapy had been discontinued.

CASE 4. W. L., eighty-eight years old, was known to us for four years prior to this study. He was deaf and past history was not well documented, but he

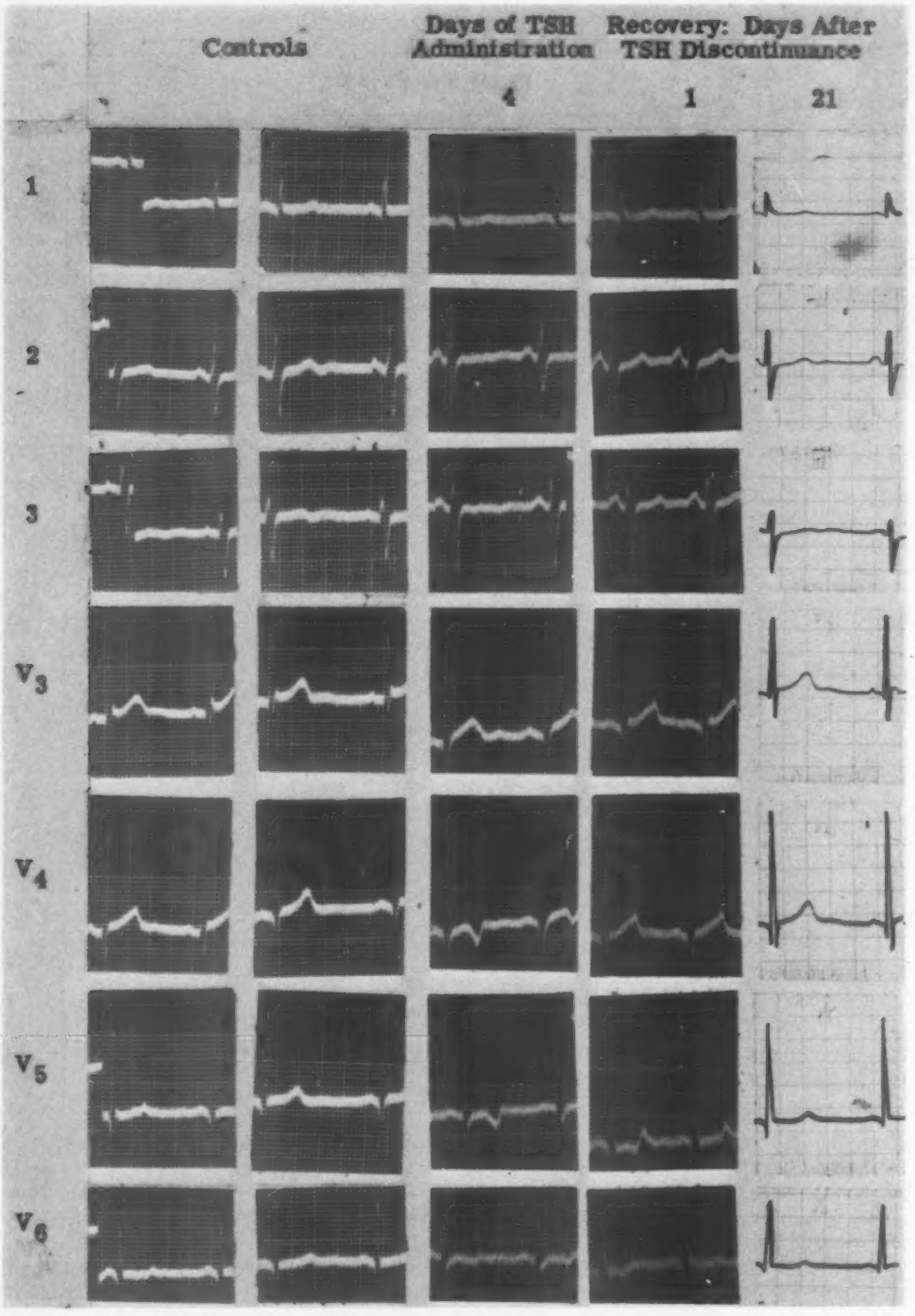

FIG. 2. Case 3. Effect of TSH on the electrocardiogram. The earlier of the two control tracings is omitted from Table II. After four days of administration of TSH, there were striking changes: coving and depression of the RS-T segment, with diminution and inversion of T in leads V_4 to V_6.

had been observed to have mild emphysema with frequent recurrences of mild lower respiratory infections. His cardiac index was 1 9 L./min./M², which is low. The circulation time (arm-to-tongue) was twenty-eight seconds. Atrial and venous pressures were normal. On roentgenographic examination there was extensive calcification of the arterial system. Cardiac size had not increased during the preceding three years and was less than 15 per cent greater than the mean normal value. Pulmonary functional impairment was evidenced by a maximum breathing capacity of 38 L./minute, vital capacity of 2.4 L. and a total lung capacity of 5.7 L.

Electrocardiogram control records (Fig. 3), taken

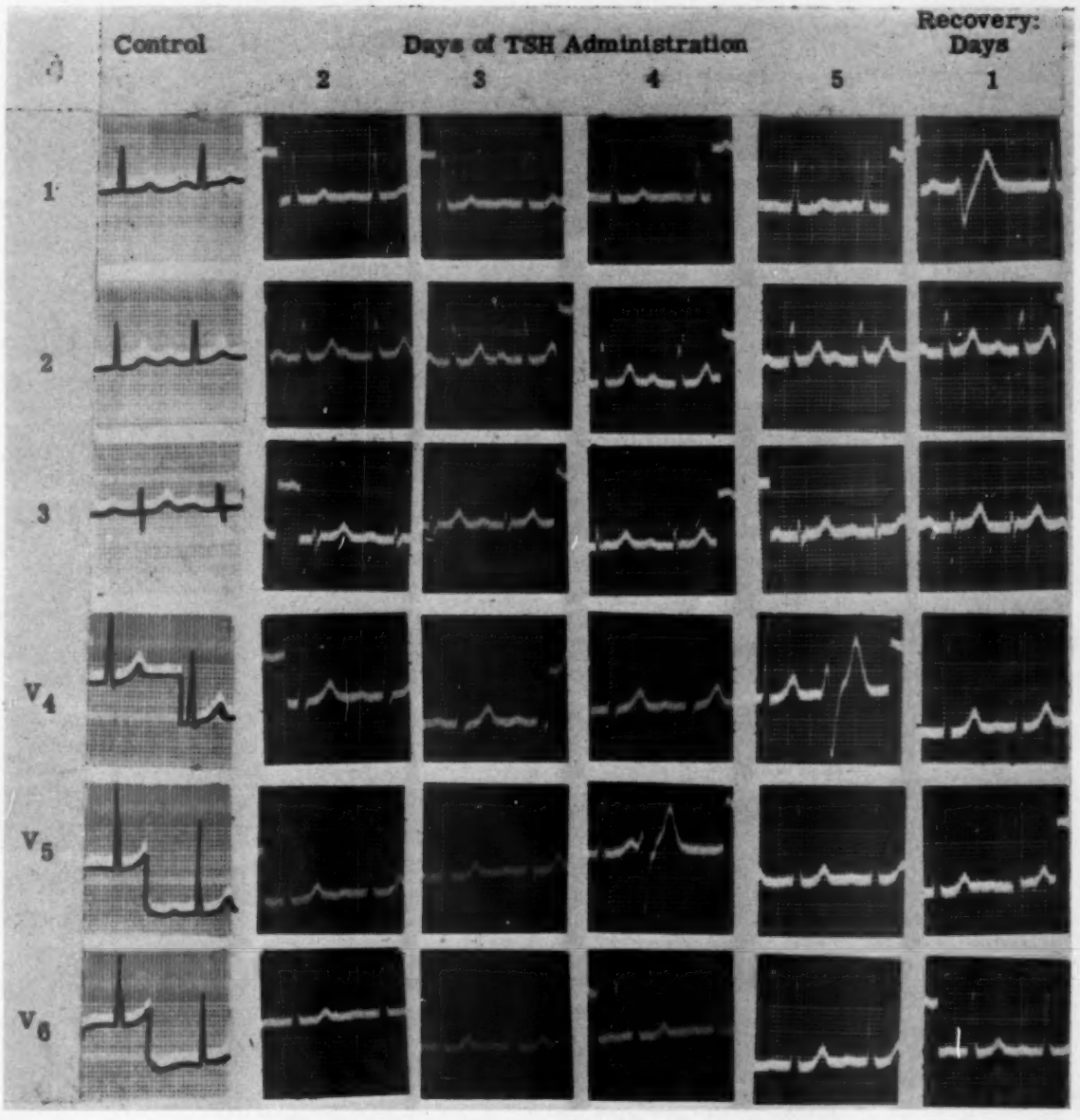

FIG. 3. Case 4. Effect of TSH administration on electrocardiogram. The earlier of two control records, described in Table II, is omitted from the figure. After four days of TSH administration, premature ventricular systoles (broad, with peaked T waves) appeared which did not diminish until eight days after TSH was discontinued. Little change in heart rate was noted throughout the series. A record taken six days after the withdrawal of the drug, described in Table II, is not included in the figure.

three months and again several days prior to TSH administration, did not differ significantly from a record taken three years before, except for P-R prolongation to 0.24 second in the earlier of the two control records. Occasional premature atrial systoles were noted.

In an electrocardiogram taken after two days of TSH administration (Fig. 3), premature atrial systoles appeared. The P-R interval did not change significantly. After three days of TSH administration, S-T revealed minimal depression in leads I, V_5 and V_6. After four days of TSH treatment (the subject received five doses of TSH), premature ventricular systoles appeared in the record for the first time. They persisted, diminishing on the eighth day after TSH was discontinued. Little increase in heart rate occurred throughout the series. A record taken two and one-half weeks after withdrawal of TSH revealed persistent atrial premature beats but none of ventricular origin.

CASE 5. G. F., ninety-two years of age, was well except for a small draining sinus in the anterior chest wall, the result of an abscess of unknown causation. There was slight cardiac enlargement; transverse diameter was estimated from the roentgenogram to

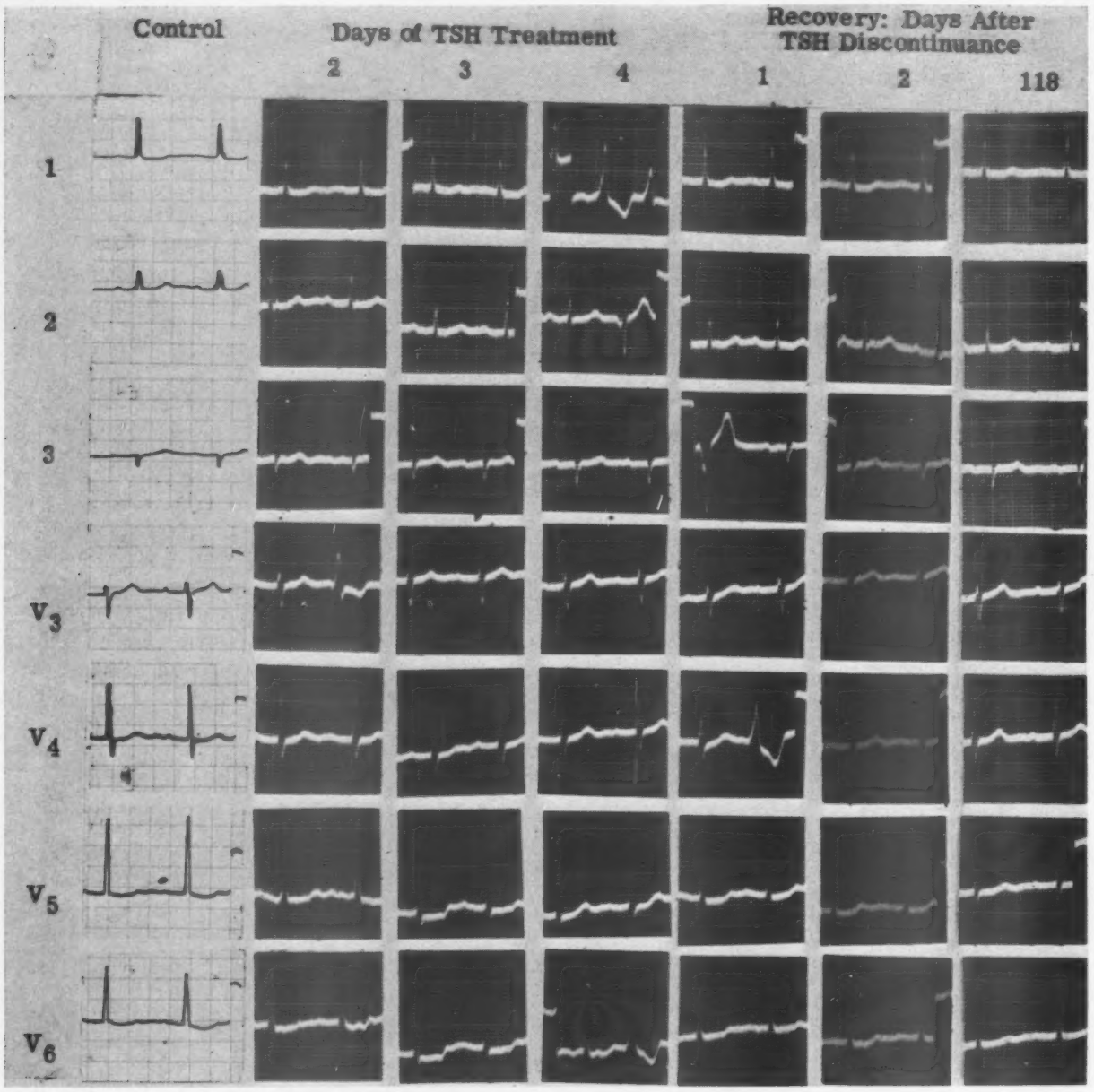

FIG. 4. Case 5. Effect of TSH administration on the electrocardiogram. The figure does not include the earlier of the control tracings described in Table II. After two days of TSH administration, heart rate had increased only slightly but premature ventricular systoles were frequent. After three days S-T was depressed and T was diphasic in V_5 and V_6. After four days of TSH, paired premature systoles occurred. Two days after withdrawal of TSH, although the basal metabolic rate was still elevated, S-T and T patterns showed a return toward control configuration.

be less than 20 per cent greater than normal, but there was a prominent left ventricular salient.

An electrocardiogram (Fig. 4) revealed first degree A-V block with a P-R interval of 0.25 second, slight depression of S-T in leads I, II, aVL and V_4 through V_6. The T waves were low throughout the tracing. A left axis deviation was present in the limb leads. A second control record showed slight S-T depression in V_4 to V_6 and T waves which were smaller in leads V_3 to V_6. In this tracing premature ventricular systoles were present. Although the control record was abnormal, the electrocardiographic response to exercise was normal.

After two days of TSH treatment the heart rate had increased only four beats per minute over the mean (73) of the control values, but premature ventricular systoles were frequent and there were runs of bigeminal rhythm (Fig. 4). After three days of TSH S-T was more depressed in V_4 to V_6 and T was diminished in V_4 and diphasic in V_5 and V_6. One day later the heart rate was 82 per minute, S-T was less depressed, T in V_4 was taller and T in V_5 was

upright. On the following day, the record was essentially unchanged, except that the premature systoles now occurred in short runs of two successive beats, the second of which varied in form. T was upright in V_4 and V_5 and slightly diphasic in V_6. S-T waves in V_5 and V_6 were less depressed. Because of the signs of ventricular irritability, TSH was withheld at this time. A day later (two days after the fourth and last dose of TSH was administered), the heart rate was 82. There was no noteworthy change in the electrocardiogram except that the premature systoles occurred singly and in runs of bigeminal rhythm. On the following day, although the basal metabolic rate was still elevated, the S-T and T patterns showed a return toward control configuration. A record taken three months later did not show any premature ventricular beats.

Comments

Four of five subjects showed definite abnormalities of electrocardiographic pattern during and immediately following the period of TSH administration. These abnormalities were evidences of increased irritability and altered repolarization. No pattern of QRS change occurred; and although the pattern of T wave inversion was "coronary type" in two cases, there was no evolution to show injury currents, protracted myocardial insufficiency or infarction. Sedimentation rate did not change, and serum glutamic oxalacetic transaminase, assayed in four subjects, did not become abnormal.

In Case 1 it may not be justifiable to ascribe observed abnormalities to the administration of TSH, since the changes were demonstrated to a variable degree after the drug was discontinued (only a single control record was available for this case). In Case 2 the electrocardiographic variations reflect no differences ascribable to TSH, and there was no evidence of increased irritability. In two of the remaining three cases T wave inversion and evidences of increased irritability occurred. Since none of the subjects can be said to be free of underlying cardiac disorder, the observed alterations in the electrocardiograms may not accurately represent the response to TSH to be expected in "normals." To the extent that our observations reflect the high incidence of cardiovascular abnormalities in older individuals, however, they are not an unfair picture of the patient who might receive TSH on clinical grounds.

Causes of Electrocardiographic Alterations: It was surprising that the electrocardiographic alterations were manifest early in some cases before there were marked increases in heart rate (Cases 3 to 5) or basal metabolism (Cases 1 and 5). Regression of electrocardiographic changes was noted, even though the basal metabolic rate was rising or at maximum observed value (Cases 1, 3 and 5). Inasmuch as the time of electrocardiographic alterations did not correspond to changes in heart rate and basal metabolism, the possibility is suggested that the electrocardiographic alterations need not be the result of increased metabolic demands on the heart associated with thyroid stimulation or increased body metabolism.

An early increased irritability and altered repolarization of the myocardium could be due to several other possible causes, singly or in combination: (1) TSH may have some direct effect upon the heart. (2) Cardiac effects of TSH might be mediated by the thyroid and represent the known effect of thyroid hormone on the heart, secondary to the increased cardiac metabolism and to the increased demands upon the heart of an increased total metabolism. They may appear temporally out of phase with changes in basal metabolic rate or heart rate because they may be more readily evoked during a change in circulatory requirement or cardiac performance before cardiac adaptation is optimal. (3) Since the changes observed following TSH administration resemble the effects of adrenergic agents in some respects, it is possible that these effects are due to sympathetic or sympathomimetic effects of thyroid hormone.

We are aware of no evidence which would support the first possibility. Starr and Liebhold-Schueck[6] have reported electrocardiographic changes occurring during the treatment with thyroxine isomers of five patients who had myxedema. TSH was given to several of these patients (15 mg. on each of three successive days) and did not appear to affect the electrocardiogram in the absence of functioning thyroid. These authors report that the alterations in the electrocardiogram which occurred during thyroid substitution therapy tended to precede metabolic effects, and suggest that the change in the electrocardiogram represents a pharmacodynamic effect of these preparations. These observations and ours support the second and third possibilities.

Sympathomimetic Effects of TSH Administration: That increased metabolic effects of thyroid hormones may lag behind the electrocardiographic effects is in accord with a body of experimental evidence suggesting that thyroid

hormone can potentiate the physiologic activity of epinephrine and norepinephrine. This has been given experimental support by studies in dogs in which sympathetic activity has been blocked,[7] and in rats after surgical ablation of the adrenal medulla.[8] Surtshin et al.[9] dispute the hypothesis that the metabolic changes of thyrotoxicosis are due to augmented physiologic effects of epinephrine or norepinephrine, reporting that neither adrenergic blockage nor adrenal demedullation would negate the calorigenic action of thyroxine in rats. This does not, however, argue against sympathomimetic effects of thyroid hormone. Since the electrocardiographic effects in the subjects occurred early and with doses of TSH that were not excessive, it may be possible to test the hypothesis that some effects of thyroid hormone are mediated via sympathetic mechanisms in the euthyroid human. That the interrelationships are not simple, however, is apparent from the variety of metabolic and cardiovascular effects of epinephrine in even the hypophysectomized animal. Of interest, further, is the suggestion from the work of Ackerman and Arons[10] that epinephrine exerts a direct effect on the thyroid in activating secretion by the gland, although stimulation of the anterior pituitary-thyroid axis has not been ruled out as a possible mechanism for epinephrine-induced release of thyroid hormones.

Summary

In three of five men, aged forty-six to ninety-two, the intramuscular administration of 25 mg. (10 U.S.P. units) of thyroid stimulating hormone (thyrotropin; TSH) on each of four or five successive days, produced electrocardiographic evidence of changes in myocardial irritability and repolarization which appeared and declined early in relation to change in heart rate and basal metabolic rate.

The nature and time course of these changes may provide information on the mechanism of thyroid stimulation of the heart, and are compatible with an hypothesis that thyroidal effects on the heart are, at least in part, mediated by a sympathomimetic mechanism. Other explanations are not excluded. The observations are of clinical interest and may suggest a test of the above hypothesis in man.

Acknowledgments

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Retrograde Catheterization of the Left Ventricle in Aortic Stenosis*

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THE DIRECT determination of pressure in the left ventricle is of great value in examining patients with valvular disease of the left heart and in establishing surgical indications. There are three methods in current use: (1) transbronchial puncture of the left atrium[1,2]; (2) percutaneous puncture of the left atrium.[3,4] In these two methods a catheter is passed through the needle into the left ventricle. (3) Direct puncture of the left ventricle is the third method.[5–24]

In comparing the results of these technics for reaching the left ventricle, we find that transbronchial puncture of the left atrium has a low morbidity and mortality; a fatal outcome is reported only sporadically.[12] Morrow,[13] who collected data on 1,200 cases, reports no mortality. Bronchoscopy, however, is an unpleasant method of examination and it is difficult to get the patient under basal conditions. Soulié[14] reports that in thirty-one transbronchial punctures the left atrium was not reached in seven instances and that in the twenty-four successful punctures the left ventricular pressure could be estimated only fourteen times. Our own experience points in the same direction.

There are a great number of publications[15–21] on percutaneous puncture of the left atrium. Its disadvantage is that the examination must take place in the lateral or ventral position which may cause hemodynamic changes.[21] Furthermore, this method is not without risk. In the series of Musser and Goldberg,[19] who did 450 punctures of the atrium, there were various complications in sixty-three patients, four of whom died. Bougas[22] collected 1,770 cases from the literature and found a mortality of 0.5 per cent. In his own series of 220 cases one patient died. In Bailey's series[23] of 700 examinations five patients died. There were a few fatal cases in various small series.[17,18–20] Moreover, the left ventricle was not always reached by this second method. Blakemore,[20] in a series of fifty-one patients, was unable to get into the ventricle of six patients. In his series there was one death and serious complications occurred in two patients. He concluded that "the routine use of this method is not warranted. It seems advisable to perform the study only when an experienced thoracic surgeon is available."

Experience with the direct percutaneous puncture of the left ventricle is more limited. In the first series of thirty-four patients Brock[5] had no complications. Fleming et al.[24] reported two deaths in 158 examinations. The number of slight complications, such as pericardial effusion, was small. In eight cases of their first series of thirty-six patients, the catheter which was introduced through the needle in the left ventricle did not reach the aorta. The aorta was reached twenty-three times in the second series of forty-three patients. Fleming et al. concluded that the procedure was dangerous in patients considered bad risks; they advised doing this examination only when subaortic stenosis is suspected and there is no calcification of the valves.

In view of the results obtained by these three methods of reaching the left ventricle, it would be desirable to have a simple method which involves only small risk to the patient when determining the pressure in the left ventricle under basal conditions and allowing catheterization of the right heart at the same time in order to estimate the cardiac output. While making thoracic aortographies with the method of Jönsson[6] we were struck by the fact that often the catheter easily went through the aortic valve into the left ventricle without causing

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TABLE I
Results of Catheterization of the Left Ventricle in 150 Patients

Type of Stenosis	Patients (no.)	Left Ventricle Reached (no.)	Success (%)
Not severe	120	93	77
Severe	30	20	66

TABLE II
Comparison of Results in Two Groups of Patients

Stenosis Present	Group I 1955–1956 (40 Cases)		Group II 1956–1958 (110 Cases)	
	Success (62.5%)	Failure (37.5%)	Success (80%)	Failure (20%)
None	10	—	36	—
Slight	9	—	38	—
Slight or none	—	11	—	16
Severe	6	4	14	6
Totals	25	15	88	22

complications. In view of this we investigated whether retrograde catheterization of the left ventricle from a peripheral artery was a method suitable for clinical use in the examination of patients with possible stenosis of the aortic valves.

METHOD

The patient lies on his back and under local anesthesia the brachial artery at the bend of the elbow is exposed by a small transverse skin incision, splitting the lacertus fibrosus if necessary. After a specimen of arterial blood has been taken, the puncture in the arterial wall is held open with a narrow vein hook and a thin Cournand catheter (5 or 6F.) is inserted into the lumen and directed proximally. The catheter is irrigated with a dilute solution of heparin, pushed into the ascending aorta and followed radiographically. Turning the left shoulder of the patient a little forward causes the catheter in the ascending aorta to be more visible.

Watching the tracing on the cardioscope, the examiner moves the catheter to and fro at the level of the aortic valves until it slips into the left ventricle. Its arrival there is shown by the appearance of the left ventricular pressure tracing. During withdrawal of the catheter a record is made of the pressures in the left ventricle and ascending aorta. At the end of the examination the opening in the brachial artery is closed with an atraumatic silk suture, No. 5-0. It is made easier by applying a sphygmomanometer. If there is a gradient between the systolic pressures of the left ventricle and the aorta, the size of the functional aortic valve ostium may be estimated with the Gorlin and Gorlin formula;[8] as the right heart is catheterized at the same time and the cardiac output is calculated.

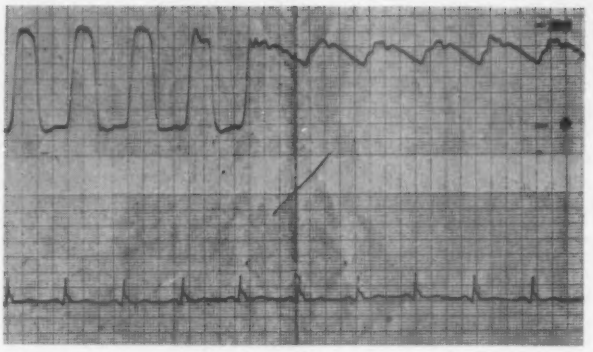

FIG. 1. Aortic stenosis: Catheter withdrawn from left ventricle into ascending aorta. Aortic systolic pressure gradient 15 mm. Hg.

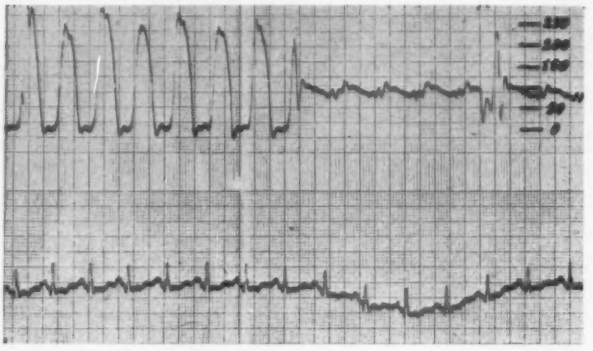

FIG. 2. Severe valvular aortic stenosis: Aortic systolic pressure gradient 130 mm. Hg. Note the pulsus alternans in the left ventricular tracing (*left*). Diagnosis confirmed at operation under hypothermia.

RESULTS

With this method 150 patients were examined from May 1955 to July 1958 (Table I). In 113 cases (75.3 per cent) the catheter reached the left ventricle; in thirty-seven cases it was not possible to pass the aortic valves. In the one hundred thirteen successful cases the following were noted: (1) No gradient was found at the aortic ostium forty-six times. Therefore, there was either no stenosis at all or the damage to the aortic valves was so slight that no hemodynamic effect could be measured under basal conditions. (2) A systolic gradient of 5 to 25 mm. Hg was measured forty-seven times. These were regarded as patients with a moderate degree of aortic stenosis which did not come within the scope of surgical treatment

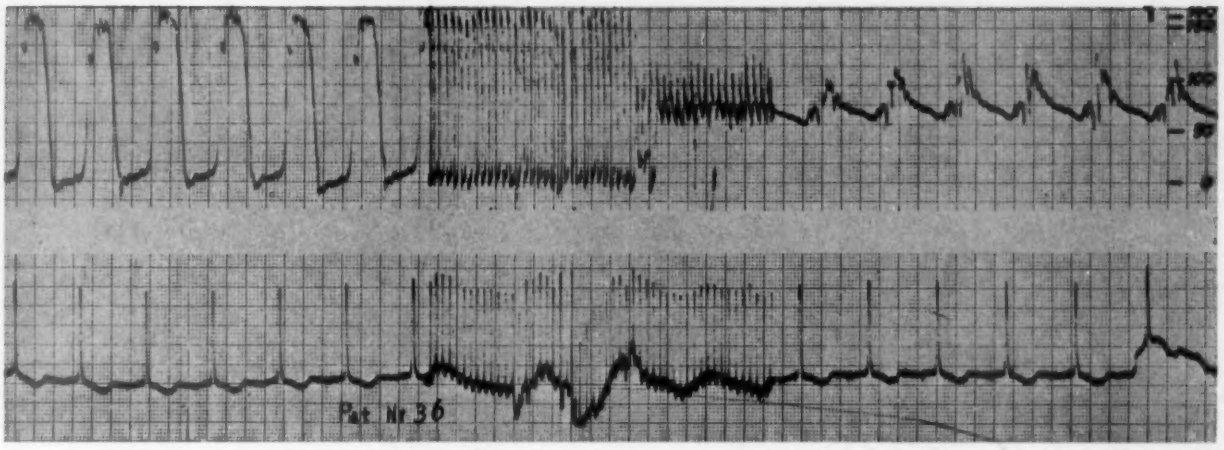

FIG. 3. Moderate valvular stenosis: Systolic pressure gradient 55 mm. Hg. Diagnosis confirmed at operation.

(Fig. 1). (3) Twenty times a gradient of 30 to 150 mm. Hg was measured which was taken to indicate severe aortic stenosis. These patients were all treated surgically (Figs. 2 and 3).

As stated before, we did not succeed in estimating the severity of the stenosis in thirty-seven cases. We concluded on other grounds that ten of them had severe stenosis; these patients were also treated surgically and our suspicions were confirmed at operation.

The percentage of successful catheterizations increased with our experience (Table II). In the first group of forty patients[7] we succeeded in measuring the left ventricular pressure in twenty-five or 62 per cent. In the second group of 110 patients we were successful in eighty-eight or 80 per cent.

Complications

In our series of 150 patients there were no serious complications that could be ascribed to the examination itself. There was no mortality. The route via the brachial artery involves no risk of a disturbance to the circulation in the forearm because of the extensive network of collaterals—the so-called rete articulare cubiti.

To avoid damage we always use smaller catheters than the lumen of the vessel allows. In this manner we also avoid arterial spasm which is difficult to suppress with drugs. Thus, the manipulation with the catheter is made easy. The radial artery remained palpable at the wrist except in four cases. Nevertheless, these patients had no disturbance of the circulation in the forearm. Only once did a knot appear in the catheter, following which the catheter could be removed from the artery with caution. Disturbances of cardiac rhythm rarely occurred; this suggested that such disturbances arise less frequently during retrograde catheterization of the left ventricle than during catheterization of the right ventricle.

We did not see embolic phenomena in the brain or elsewhere, e.g., detachment of calcifications of the aortic valves. On some occasions the catheter entered a coronary artery. This was proved by x-ray examination; the catheter was well inside the shadow of the left ventricle and at the same time no left ventricular pressure was visible on the tracing. When this occurred, we never found alterations suggestive of myocardial infarction in the electrocardiogram.

Comments

Zimmerman et al.,[9] who tried retrograde catheterization in 1949, used the left ulnar artery as the route of approach. In five patients with normal aortic valves they did not succeed in catheterizing the left ventricle. They were successful, however, in eleven patients with syphilitic aortic insufficiency. In their opinion the catheter could not pass through normal valves because of the short ejection period of the left ventricle. One patient with rheumatic aortic insufficiency died from ventricular fibrillation. At autopsy, however, no traumatic damage was found either in the aorta, the coronary arteries or in the left ventricle. In another patient, who died four days after examination, no lesions due to the procedure were discovered at the postmortem examination.

Lason et al.[10] first tried retrograde left ventricular catheterization in dogs and showed its harmlessness. They then reported success

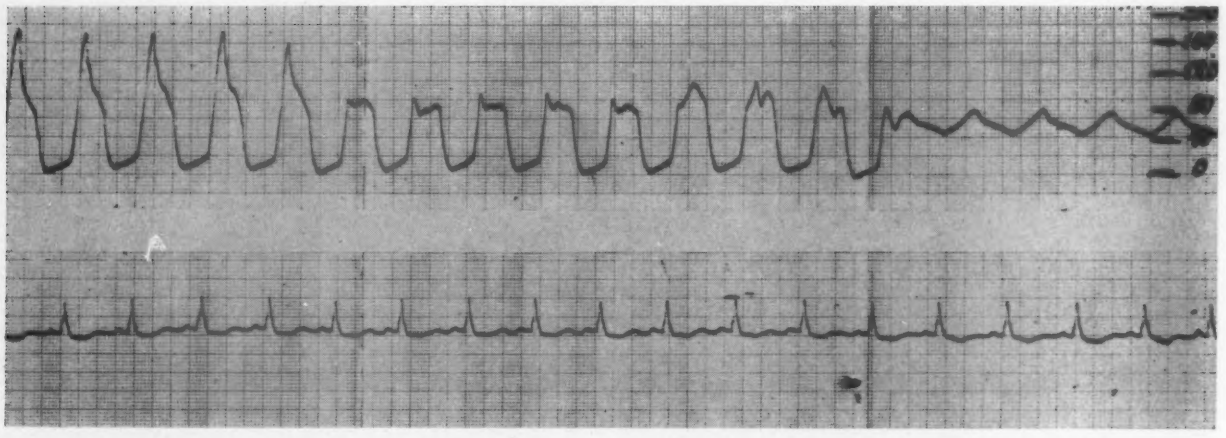

FIG. 4. Subvalvular aortic stenosis: While the catheter is in the infundibulum (midportion of curve) the systolic pressure is the same as in the aorta (right) and the diastolic pressure is the same as in the left ventricle (left). At transaortic operation under hypothermia a diaphragm was found 1 cm. under the normal aortic valves.

in seventeen patients, none of whom showed complications. They recorded both intracavitary pressures and electrocardiograms. Wilder et al.[11] carried out tests with direct angiocardiography of the left ventricle. In twenty dogs the aortic valves were easily passed by the catheter. They concluded that the injection of contrast material into the left ventricle by way of retrograde catheterization was apparently safer than by way of direct puncture of the left ventricle.

Although results of retrograde catheterization as recorded in the literature were not unfavorable, the general opinion seems to be that this method is impractical and even dangerous. From our experience with 150 patients it appears that the risk is very small. There is an 80 per cent chance of reaching the left ventricle. The simplicity of the method is its chief advantage; it can be carried out simultaneously with catheterization of the right heart and through the same skin incision.

We prefer to do retrograde catheterization using the right arm, because the catheter passes more easily into the ascending aorta through the innominate artery than through the left subclavian artery. It is possible to do this catheterization using the left arm, but the chances of failure are much greater as the catheter sometimes keeps going into the descending aorta. In our clinic, therefore, the routine procedure is to do catheterization of the right heart through the right arm if exploration of the left heart is contemplated, e.g., in the study of patients with mitral stenosis when it is often important to measure the diastolic pressure in the left ventricle.

In patients with severe aortic stenosis we succeeded in reaching the left ventricle in only 66 per cent of the cases. In studying patients with aortic stenosis, however, it is always necessary to introduce a catheter into the ascending aorta in order to measure the gradient. There may be unpredictable differences in the systolic pressures between a peripheral artery and ascending aorta. It seems logical to attempt first to pass the aortic catheter through the aortic valve; the left ventricular pressure can then be assessed without further intervention. In case of failure other methods for reaching the left ventricle may be tried if it should be necessary to know the differences in systolic pressure between the ascending aorta and the left ventricle.

Another advantage of retrograde catheterization is that the existence of subvalvular aortic stenosis can be proved before operation. This happened three times in our series and the diagnosis of subvalvular aortic stenosis was confirmed at operation (Fig. 4). In our series of 150 patients there was one who showed the clinical picture of aortic stenosis and in whom supravalvular aortic stenosis was believed to exist from the findings at left heart catheterization.[25] This diagnosis was confirmed at thoracotomy.

SUMMARY

In 150 patients suspected of having aortic stenosis, retrograde catheterization of the left ventricle through the right brachial artery at the bend of the elbow was attempted. In patients with severe aortic stenosis we succeeded in reaching the left ventricle in 66 per cent of the cases; this percentage rose to 77 per cent

in patients who had only a slight stenosis or none at all. The examination was combined with catheterization of the right heart under the same basal conditions and with simultaneous determination of the cardiac output. Thus, the size of the functional aortic valve ostium could be measured with the aid of the Gorlin and Gorlin formula. In our series there was no mortality; cardiac complications or disturbances of the circulation in the forearm need not be feared.

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An Electrocardiographic Study of High Take-Off of the R(R′)-T Segment in Right Precordial Leads

Altered Repolarization*

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REPOLARIZATION of the heart muscle restores the transmembrane potential to a normal resting level. In the electrocardiogram repolarization starts immediately after the initial deflection has ended and is represented by the R(S)-T segment. This segment is very frequently exactly at the zero level. Slight R(S)-T segment deviations do occur in the presence of a perfectly normal cardiac status. With respect to the chest leads this has been found to affect mostly the mid- and left-sided leads; the shape is concave upward terminating in a high positive and peaked T wave. This finding is commonly referred to as a physiologic variant; there is a fairly extensive literature available on this topic (newer references are Bedford and Thomas,[1] Chelton and Burchell[2]). However, physical characteristics of the amplifying type of electrocardiograph (top of the upper frequency limit) may play a role; in a study in which two types of electrocardiographic machines are used, the incidence of elevated and arched S-T segments was found to be 0.29 and 24.3 per cent, respectively.[3]

This study refers to a particular pattern that is essentially characterized by an elevation of the R-T segment in the right precordial leads. It has been described before as a pattern simulating acute myocardial injury[4], as a probably normal variant,[5] and as a finding without definite evidence of organic heart disease.[6] These authors demonstrated the absence of heart disease in their patients.

CASE REPORTS

CASE 1. This white man, age forty-six years, had a bleeding duodenal ulcer for which surgery was being considered. His effort capacity had been good. No abnormality was noted with respect to the chest, heart and blood pressure. The hemoglobin was 11.5 gm. per cent. The electrocardiogram is shown in Figure 1. The patient improved on medical management and was feeling well three years later.

CASE 2. This white woman, age thirty-seven years, had a routine electrocardiogram prior to an operation for cholelithiasis. Her effort capacity was satisfactory. She was tense and anxious and obsessed with thoughts about heart disease. Nothing of significance was noted with respect to chest, heart and blood pressure. A number of laboratory studies were normal except for the calcium level which, when determined at a time when the patient was icteric, was reported as 8.7 mg. per cent. Two electrocardiograms taken at an interval of three months are shown in Figure 2. Another record taken three years later was identical.

CASE 3. This white man was observed from age thirty-five to forty-five years. He was first seen because a physician had mentioned to him the possibility of an "athlete's heart." This caused concern to the patient and when climbing stairs, transient pains developed under the left clavicular area. His effort capacity had been good. He was emotionally tense. Nothing of significance was noted with respect to chest, heart, blood pressure and laboratory data. The patient continued to be in good general health, exhibited good effort capacity and ten years later the status of the heart and blood pressure had remained unchanged. Four electrocardiograms were taken; two are shown in Figure 3.

CASE 4. This white man was observed from age fifty-six to fifty-nine years. He had been treated for duodenal ulcer previously. His blood pressure had

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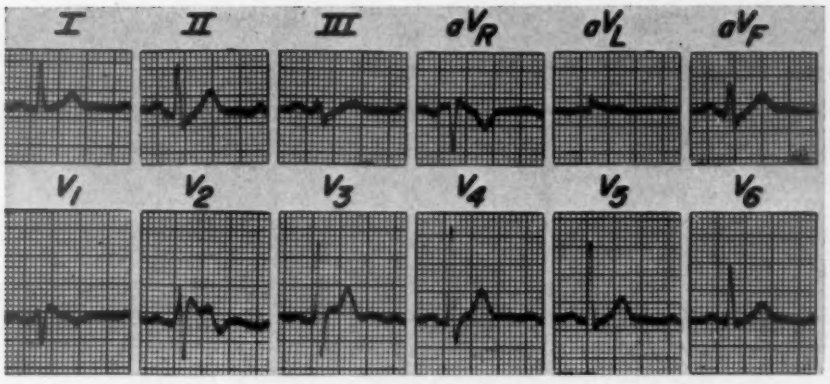

FIG. 1. Case 1. The width of the initial deflection does not exceed 0.11 second, the intrinsicoid deflection, as measured in V_2, is 0.04 second, and it is the same for V_6. There is an R′ in V_1, V_2 and aVR; there is no S in I and V_6. J is slightly depressed in II, III, aVR and V_6, and slightly elevated at aVR. R-T is elevated in V_1 to V_3 with a saddle-like deformity in the former two leads; R-T is also elevated in aVL. T is negative in V_1 and V_2 and diphasic in aVL. Q-T measures 0.37 second in II, the upper limit of normal for a rate of 83/minute being 0.368 second.

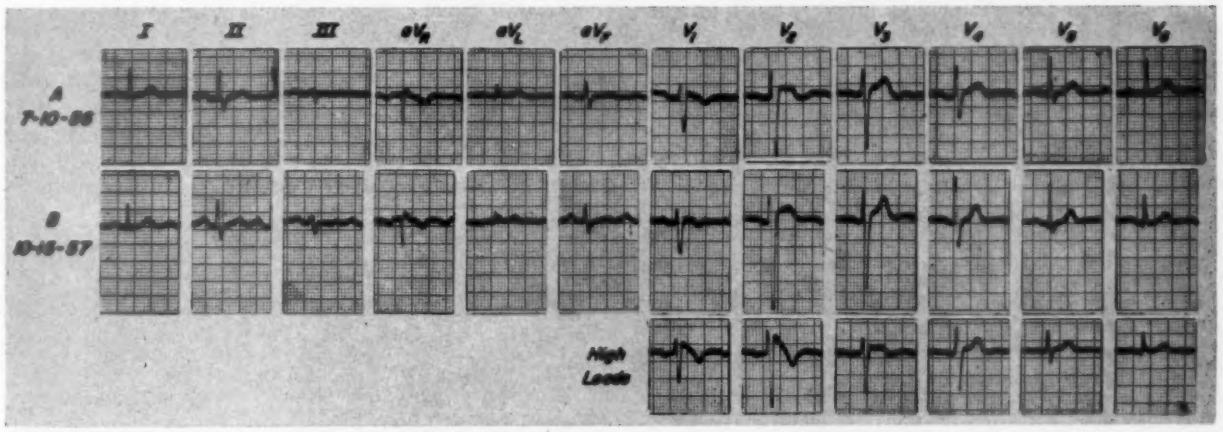

FIG. 2. Case 2. The findings obtained fifteen months apart were similar. The width of the initial deflection does not exceed 0.11 second, the intrinsicoid deflection, as measured in V_2 and V_6, is 0.03 second. There is an R′ in V_1, V_2 and aVR, and there is a minimal S in I and V_6. R-T is elevated in V_1 to V_3 and this is more evident in leads taken at a higher level, the elevation extending to position 4. T is negative in V_1 and V_2 and in high V_1 to V_3. Q-T measures 0.40 second in II, the upper limit of normal for a rate of 71/minute being 0.403 second.

been normal. Two electrocardiograms taken at another hospital when the patient was forty-nine years old were identical and were reported as showing intraventricular conduction defect, with involvement of the posterior wall of the left ventricle. His effort capacity had been good. An electrocardiogram was taken on admission to the hospital because of nausea and drowsiness. There had been no chest pain. Examination of chest, heart and blood pressure revealed nothing of significance and the laboratory data were normal. Because of the abnormal features of the electrocardiogram, cardiac infarction was suspected and the patient was given an anticoagulant (Hedulin®). The possibility that the abnormal electrocardiographic findings might be secondary to an acute cerebral injury was mentioned. Anticoagulant therapy then was stopped. An electroencephalogram suggested subcortical involvement. Neurologic signs had become more marked and the diagnosis was partial thrombosis of the left middle cerebral artery. The patient recovered and remained active, showing good effort capacity and normal findings with respect to heart and blood pressure. Three of eight electrocardiographic studies done in the course of three years are shown in Figure 4.

CASE 5. This Negro man, age forty-two years, had an electrocardiographic study because of chest pain. His effort capacity had been good. For a period of several days he had had lack of appetite, upper abdominal pain and a few episodes of vomiting. Then a sharp painful sensation appeared below the left nipple area and over the precordium; there was no

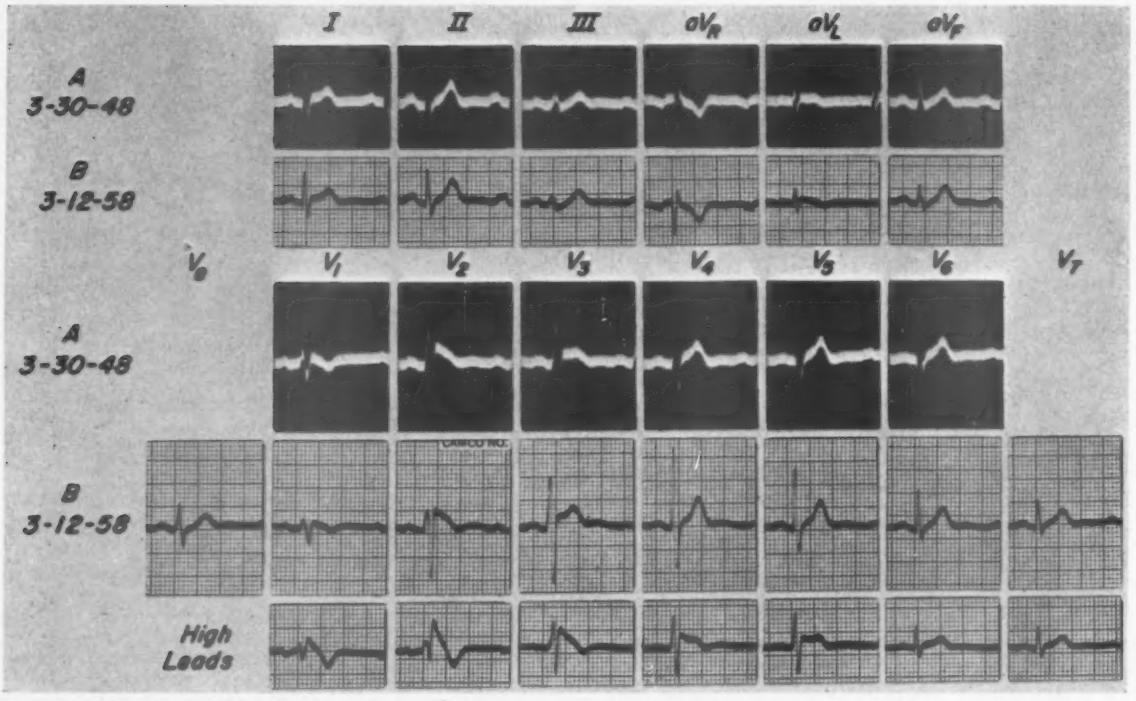

FIG. 3. Case 3. The findings obtained ten years apart are essentially the same. P is slightly notched. The width of the initial deflection is 0.11 second; the intrinsicoid deflection as measured in V_2 is 0.03 second. There is an R′ in V_1, V_2 and aVR, and there is an S in I and V_6 and V_7. J is depressed in III. R-T is elevated in V_1 to V_3 and slightly in V_4; it is elevated in high V_1 to V_5 with a suggestive step like deformity in several of the leads. R-T is elevated in I and aVL. T is negative in V_1 and V_2, in high V_1 to V_4 and in aVL. Q-T measures 0.34 second in II, the upper limit of normal for a rate of 78/minute being 0.38 second.

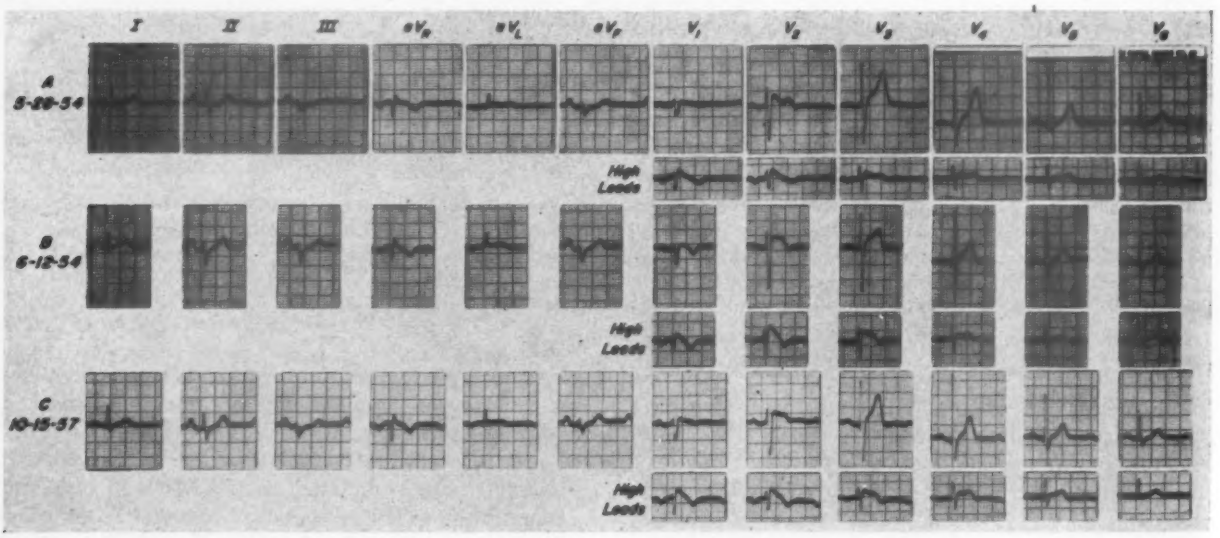

FIG. 4. Case 4. The findings obtained at intervals of two weeks and of three years and four months, respectively, are similar. The width of the initial deflection is 0.09 to 0.10 second; the intrinsicoid deflection as measured in V_2 is 0.02 second and is 0.03 second for V_6. There is an R′ in V_1, V_2 and aVR, and there is a small S in I and V_6. J is depressed in III and aVF. R-T is elevated in V_1 to V_3 and in high V_1 to V_3, with a suggestive saddle or step like deformity in several of the leads. R-T is also elevated in aVL. T is negative in V_1, slightly so in V_2, and negative in high V_1 to V_2. Q-T measures 0.44 second in III, the upper limit of normal for a rate of 56/minute being 0.433 sec.

substernal location, no radiation and no aggravation by breathing. No abnormalities were noted with respect to the chest, heart and blood pressure. There was no fever or leukocytosis and the sedimentation rate was 23 mm./hour. Five electrocardiograms were recorded in the course of nine days; two are shown in Figure 5. The patient was well subsequently.

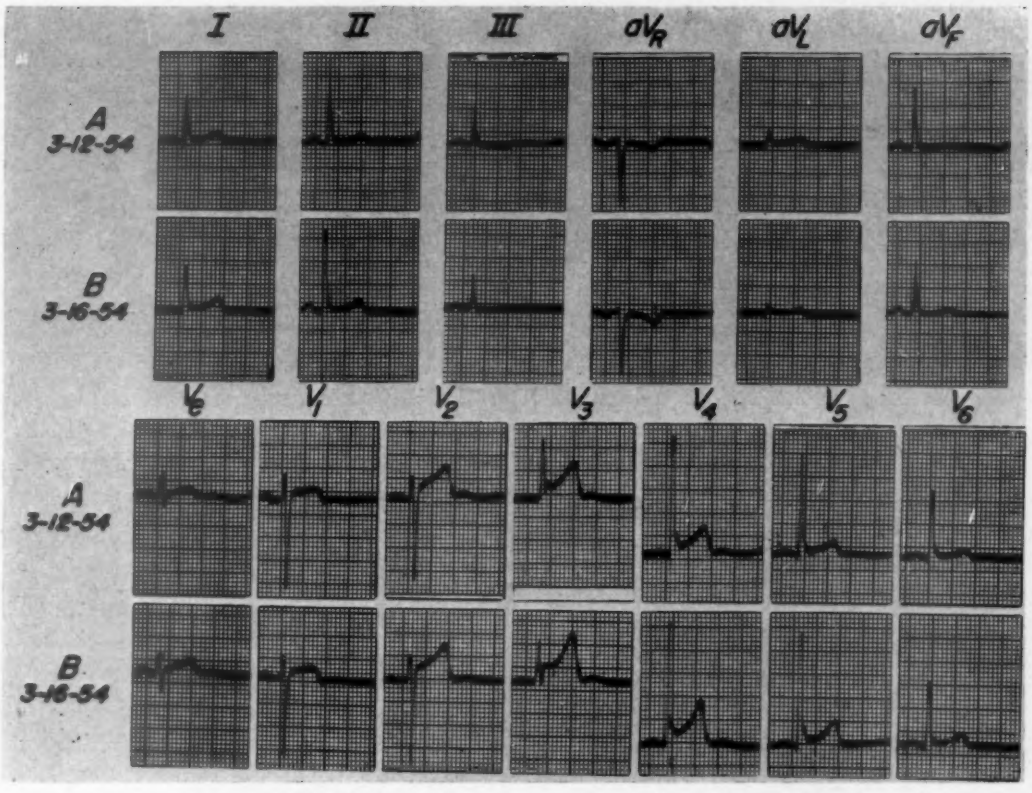

FIG. 5. Case 5. The findings obtained four days apart are nearly identical. The width of the initial deflection does not exceed 0.11 second, the intrinsicoid deflection as measured in V_2 is 0.02 second and it is 0.04 second in V_4. There is a minimal R′ in V_1,V_2, none in aVR, and no S in I and V_6. J is slightly depressed in III. R-T is elevated across the whole precordium, more so over the right side, showing a peculiar straight shape. R-T is also slightly elevated in I and aVL and there is a minimal depression of it in III and aVF. T is positive across the precordium with its second limb showing a steep descent and there is a minimal secondary negative dip in V_6, V_1 and V_2. Q-T measures 0.40 second in II, the upper limit of normal for a heart rate of 65/minute being 0.41 sec.

CASE 6. This Negro man, age forty-seven years, had a routine electrocardiogram taken, having been hospitalized for sycosis and alopecia. The effort capacity was good. Nothing of significance was noted with respect to the chest, heart and blood pressure. The laboratory studies also revealed nothing significant. Two electrocardiograms were recorded in a two month interval and are shown in Figure 6.

CASE 7. This white woman was observed from the age of forty-five to forty-nine and a half years. Four years prior to the first examination she was studied in a hospital and mention was made of an abnormal electrocardiogram. Her effort capacity was fair. She was first seen prior to operation for removal of a rectal polyp. She was highly neurotic and anxious and offered a multitude of complaints. The chest wall was thin, the heart was not enlarged and the sounds were normal. Radiologically, the waistline was slightly full, the left atrium was not prominent posteriorly and the over-all size of the heart was normal. The blood pressure was low normal. Laboratory studies revealed normal findings except for a flat glucose tolerance curve; the serum calcium level was 9.2 mg. per cent.

On repeated follow-up examinations gradual changes were observed with respect to the heart: first, the appearance of premature beats of atrial origin; later, the first apical sound became loud and snappy in character; then she complained of pounding and irregular heart action; atrial flutter had developed that was changed to atrial fibrillation by means of digitalis medication and to sinus rhythm by means of quinidine medication. Subsequently, her effort capacity diminished; the second apical sound became reduplicated and at times one could hear a minimal diastolic rumble; the lower sternum became somewhat dull to percussion. Radiologically, the heart was now moderately enlarged, showing a typical mitral configuration; the left atrium was prominent posteriorly and there was no evidence for pulmonary congestion. A minor degree of right-sided congestive failure finally appeared and there was a double liver pulse. The diagnostic impression following cardiac catheterization and angiocardiography was tricuspid stenosis and questionable mitral

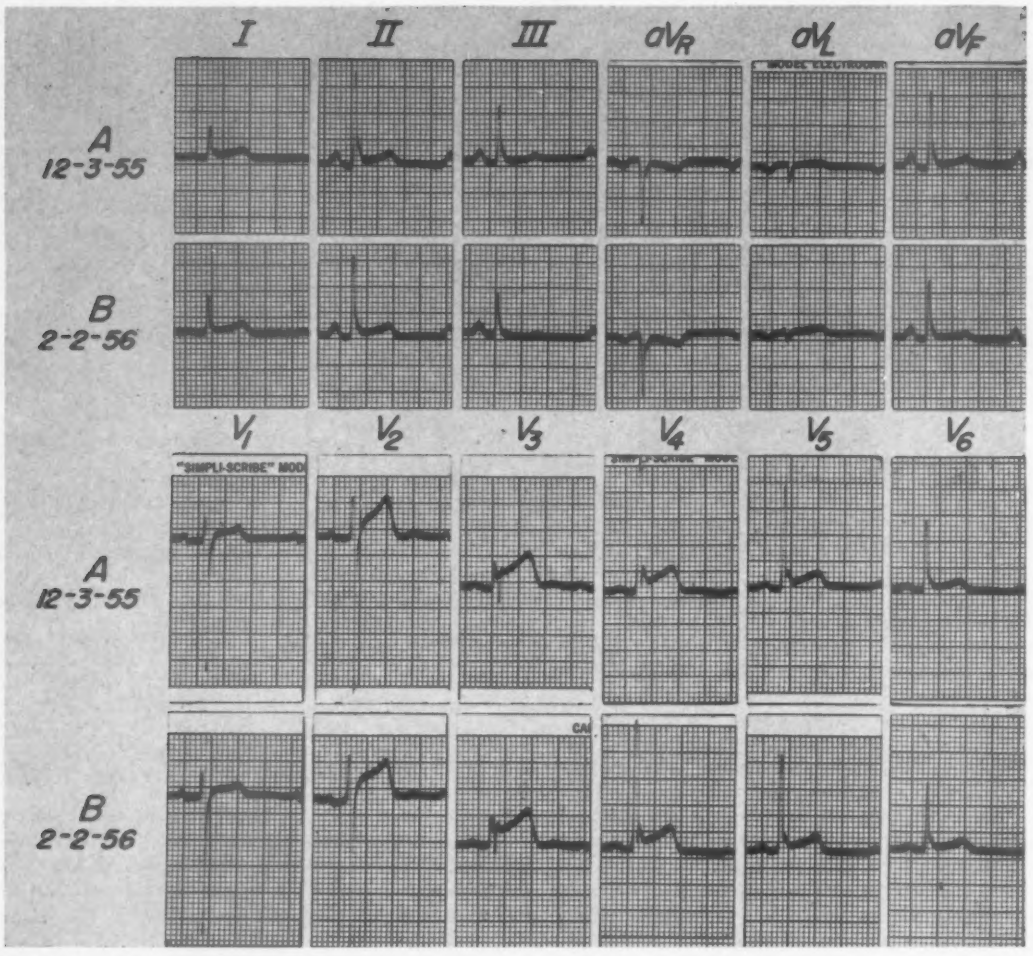

FIG. 6. Case 6. The findings obtained two months apart are essentially the same. The width of the initial deflection is 0.09 to 0.10 second, the intrinsicoid deflection, as measured in V_2 and V_6, is 0.02 second. There is a minimal R′ in V_1 and V_2, none in aVR, and there is no S in I and V_6. The voltage is increased in a number of leads. R-T is elevated across the whole precordium, more so over the right side, revealing a peculiar straight shape R-T is also slightly elevated in I. T is positive across the precordium with its second limb showing a steep descent. Q-T measures 0.36 second in II, the upper limit of normal for a rate of 71/minute being 0.392 second.

stenosis. Many electrocardiograms were taken during the observation period of four and one half years; two are shown in Figure 7. Digitalis had not been used at that time. Chest leads taken at a higher level are not shown.

CASE 8. This white man, a physician, was observed from the age of twenty-nine to forty-two years. His health in the past had been good. The family history revealed no diabetes, hypertension or angina. As an intern and resident he had had much responsibility and had overworked. He never had experienced angina of effort. One day, feeling quite fatigued, he experienced precordial pain associated with weakness and nausea of fifteen minutes' duration. The heart was not enlarged and an aortic systolic murmur of minor intensity was noted. The blood pressure was normal. The weight was 134 pounds. Laboratory studies were noncontributory, the cholesterol level was normal and the calcium level was 10.6 mg. per cent. The patient was seen several times subsequently with no new developments or findings.

One day, while in the Army, precordial pain of about five minutes' duration developed without any preceding effort. The pain radiated to the left shoulder and for the next two and a half days a precordial pressure sensation remained. The temperature did not exceed 99°F., there was no leukocytosis and the sedimentation rate was 12 mm/hour. The murmur mentioned previously was noted again. Three electrocardiograms were taken; first the diagnosis of acute pericarditis was made and subsequently that of acute coronary insufficiency. (Inspection of these three graphs revealed them to be identical with previous tracings made by the author.) The problem was reviewed by several Army medical review boards. Temporary retirement on the basis of an old cardiac

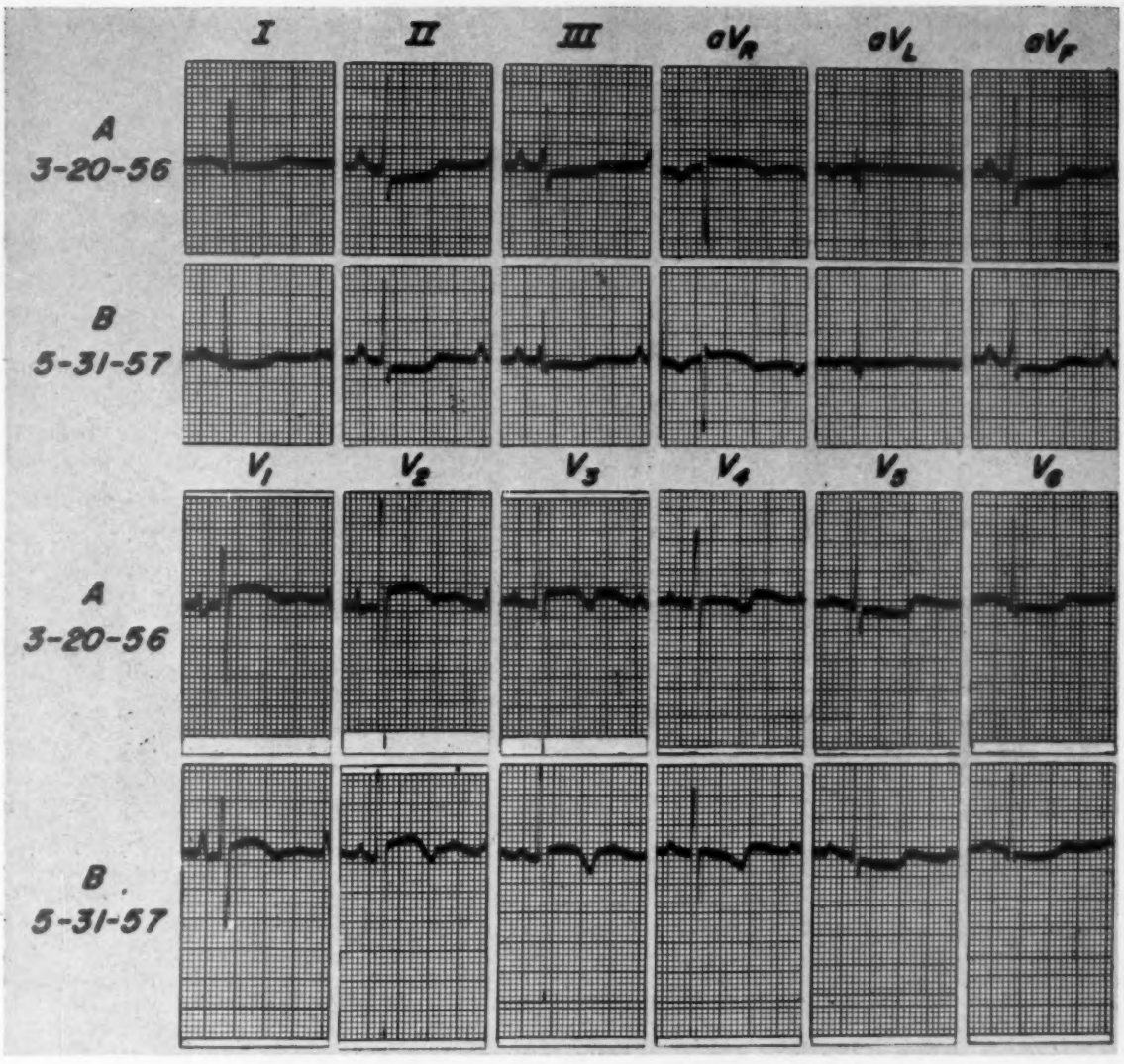

FIG. 7. Case 7. P is prominent in II, III, aVF, V_1 and V_2. The width of the initial deflection is 0.08 second; the intrinsicoid deflection, as measured in V_2, is 0.02 second and it is 0.04 second in V_6. There is a small R′ in V_1, V_2 and aVR, and there is a minimal S in I and V_6. The voltage is increased in a number of leads. R-T is elevated in V_1 and V_2 and slightly so in V_3 and aVR. R-T is depressed in I, II, III, aVF, V_5 and V_6. T is negative in V_1 to V_4, diphasic in V_5 and V_6, generally of low voltage in the limb leads. Q-T measures 0.50 second in II, the upper limit of normal for a rate of 68/minute being 0.417 sec. (A normal serum calcium level was present.) High chest leads (not shown) were identical with those taken at a regular level. This is the only case in the series revealing definite reciprocal behavior of the R(S)-T segments.

lesion aggravated by 30 per cent, was instituted; a 50 per cent disability was declared. Later, retirement disability was discontinued but he was not to return to the service. At no time was there angina of effort. He was professionally active. On being fatigued he experienced slight outer precordial pressure.

Re-examination ten years after the first examination revealed body weight 150 pounds, heart size and blood pressure normal, the minimal aortic systolic murmur unchanged and A_2 normal. Cholesterol again was normal; serum potassium was 4.2 mEq./L. and the serum sodium 140 mEq./L. The final diagnosis by the military medical board was angina pectoris with arteriosclerotic heart disease with 30 per cent disability. Three of several electrocardiographic studies are shown in Figure 8.

ANALYSIS

CLINICAL

Seven of these eight patients were studied more than once and the electrocardiographic findings were noted to be constant. None of the patients had an anginal syndrome, none had signs and/or symptoms referable to pericarditis and none of them was hypertensive. Seven patients had normal heart size; one

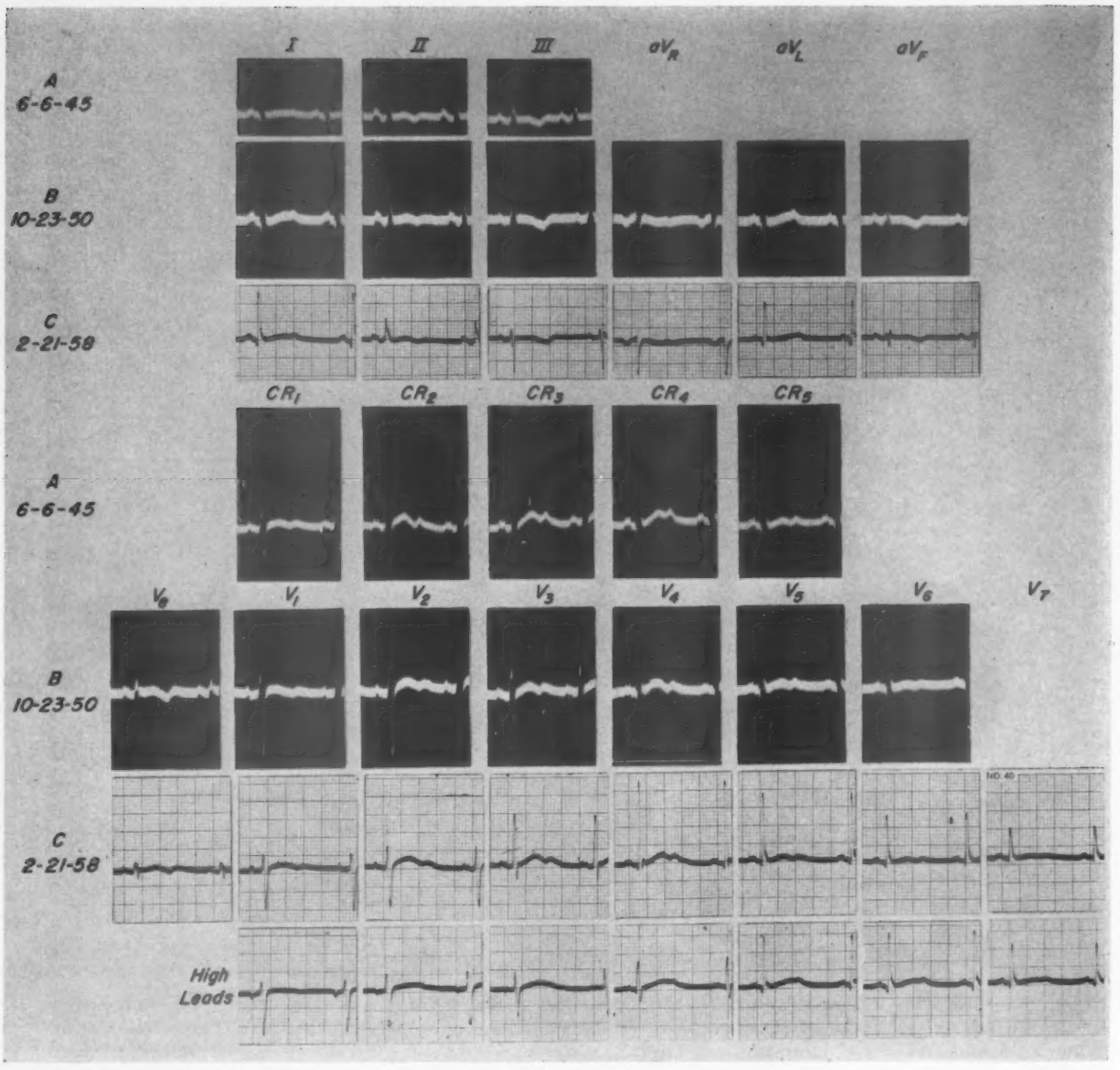

FIG. 8. Case 8. The findings obtained at intervals of five and one-half and seven and one-half years are similar. P is notched in several leads but not widened. The width of the initial deflection is 0.09 to 0.10 second. The intrinsicoid deflection, as measured in V_2, is 0.02 second and it is 0.035 second in V_6. There is practically no R′ in V_1 and V_2, none in aVR; there is no S in I and a minimal S in V_6 and V_7. R-T is slightly elevated in V_1 and V_2 and in high V_1 and V_2. T is negative in V_0, V_1 and also in II, III, aVF, the voltage is low, and there is notching in V_2 to V_6, in high V_1 to V_6 and in I. It is positive in aVL. Q-T measures 0.44 second in II, the upper limit of normal for a rate of 75/minute being 0.384 second. (A normal serum calcium level was present.)

(Case 7) began with normal heart size but heart disease developed which resulted in cardiac enlargement. There were no murmurs in six patients, one had a minimal aortic systolic murmur that did not change in the course of thirteen years (Case 8) and in one abnormal auscultatory findings developed during the course of observation (Case 7). None of the patients had received cardiac drugs. The effort capacity was satisfactory in all patients except for one (Case 7) in whom a moderate degree of effort diminution gradually made its appearance.

All patients were referred for cardiac evaluation for the following reasons: preoperative (Cases 1 and 2); skin lesion (Case 6); anxiety and compulsion, respectively (Cases 3 and 7); acute cerebral lesion (Case 4); acute abdominal distress associated with pain in the left nipple area (Case 5); and overwork associated with precordial pain unrelated to effort (Case 8).

ELECTROCARDIOGRAPHIC

All eight patients showed sinus rhythm with a rate varying from 56 to 83/minute. In one (Case 7) there was a transient disturbance of the atrial rhythm; this coincided with the development of valvular heart disease and only in this instance was the P deflection widened. P was notched in two other instances (Cases 3 and 8). The P-R interval was normal in all instances.

QRS Deflection: The width of the initial deflection varied from 0.08 to 0.11 second; significant Q deflections were not found; the voltage was noted to be moderately increased, at least in some of the leads, three times (Cases 2, and 3, 4). The intrinsicoid deflection was measured for leads V_2 and V_6, respectively. (To do this for V_1 was not found suitable in several cases because of direct transition from R or R′ into R-T.) For V_2 it measured 0.04 second in one instance (Case 1) and 0.02 to 0.03 second in the remaining seven cases; for V_6 it measured from 0.02 to 0.04 second. There were no S deflections in leads I and V_6 in three instances (Cases 1, 5 and 6); a very small S in I and V_6 were noted in three instances (Cases 2, 7 and 8), while it was clearly present in I and V_6 twice (Cases 3 and 4). Varying electrical positions were noted: semivertical (Cases 5, 6 and 7), intermediate (Cases 1, 2 and 3), semihorizontal (Case 8), horizontal (Case 4); no particular correlations could be established.

Elevated R-T Segment: The elevated R-T segment takes off over the right side of the precordium from a third portion of the initial deflection which presumably should be designated as R′ (or r′). When R′ was present in V_1, V_2 and aVR, an S was usually noted in I and V_6 with one exception (Case 1). When R′ was minimal in V_1, V_2 and absent in aVR, S was absent in I and V_6 (Cases 5 and 6) or minimal in V_6 (Case 8).

Deviation of J in the limb leads was present in seven instances (except in Case 8) and deviations of R-T, in at least some of the chest leads, were present in all cases. Special high chest leads, taken at the level of the third rib, were obtained in five instances, in three of which the degree of deviation was more marked (Cases 2, 3 and 4) while it was about the same in two (Cases 7, not shown in illustration, and 8). An upward displacement was always present over the right side of the precordium, affecting leads V_1 and V_2 once (Case 8) and leads V_2 to V_3 five times (Cases 1, 2, 3, 4 and 7). Once the elevation affected leads V_1 to V_4 (Case 5) and once leads V_1 to V_6 (Case 6). A step or saddle-like deformity was clearly noted in Cases 1, 3 and 4, and a slow ascent, associated with a steep descent of T, was noted in Cases 5 and 6. A reciprocal behavior of the S-T segments for the right and left precordial areas, respectively, was present but once (Case 7).

T Wave: The T deflection in the limb leads was generally positive in seven of eight instances in leads I, II and aVF; in aVL there were variations in directions with a definite negativity noted only once (Case 3) and here T negativity in the high chest leads extended to position V_4. In the chest leads taken at the regular level, T was diphasic in V_1 once, negative in V_1 and V_2 in five cases, negative in V_1 to V_3 in one instance. Case 5 revealed a positive direction of T across the whole precordium and Case 6 from positions 2 to 6. In five cases additional high chest leads were taken: The findings were identical with those taken at the regular level in two instances (Cases 7 and 8) while in three instances (Case 2, 3 and 4) the negativity extended one or two positions further to the left and the degree of negativity then was always more marked.

Q-T Interval: The length of the Q-T segment was measured for leads II, V_1, V_2 and V_6, in each case and compared with the predicted upper normal from a standard table. Normal findings were obtained five times (Cases 2 to 6); in one instance the upper limit was slightly exceeded (Case 1) while in two instances there was a prolongation of electrical systole (Cases 7 and 8) with normal serum calcium levels.

Comment

The common feature in this electrocardiographic pattern is a high take-off of the R(R′)-T segment over the right precordium. It is constant. Its shape varies; it may descend and often has a hump or saddle-like appearance; or it may be coved; in both instances it ends imperceptibly in a negative T deflection. Or it may ascend with a straight shape and then there is no significant T negativity. In some instances this elevation may extend, though gradually diminishing, considerably to the left. In leads taken at a higher level, the findings may be about the same, or the degree of the R(R′)-T elevation, of the T negativity and of the extension toward the left side may be more marked. A reciprocal behavior of the R-T deviations on

the right and left sides was observed but once (Case 7).

In the original description[4] comprising three cases, a right bundle branch block was considered to be an essential part of the pattern. A newer nomenclature[7] merely speaks of a delay in the excitation of the right ventricular free wall, causing the presence of a late secondary R deflection in the unipolar right arm and right chest leads. This often might be a physiologic variant. A secondary R deflection is easily diagnosed when the R-T segment takes off at the baseline but this becomes difficult when the R-T segment reveals a high take-off. Some of our graphs reveal no S deflections in leads I and V_6, and no R′ in aV_R (Cases 5, 6 and 8) and this would militate against the explanation of a delay in the excitation of the right ventricular free wall (right bundle branch block) in these cases. Furthermore, the width of the initial deflection in some of our graphs does not exceed 0.10 second (Cases 4, 6, 7 and 8).

As a matter of speculation it is assumed that this abnormal pattern is due to an unusually early onset of repolarization over the right and/or right basal side of the heart, whereby the terminal portion of QRS becomes fused with the initial portion of the R(S)-T segment.

Our own observations as well as those available in the pertinent literature indicate that this electrocardiographic pattern is compatible with otherwise perfectly normal cardiac findings; although, and as might be expected, heart disease may occasionally develop in the course of time (Edeiken[5] and our Case 7). In one patient, age seventy-nine years, the autopsy findings revealed neither cardiac enlargement nor evidence of a recent or past myocardial infarction (Stein and Weinstein,[6] Case 5).

Knowledge of this electrocardiographic pattern is of practical importance. It being rare in occurrence, its "innocence" may not be appreciated; acute myocardial injury may be diagnosed, particularly when the clinical picture includes what might simulate one of the many varieties of angina. Our Cases 4 and 8 furnish such examples. The stability of this pattern will be revealed by serial studies.

Summary

An abnormal electrocardiographic pattern of altered repolarization is described in eight cases. The common finding is an elevation of the R(R′)-T segment over the right side of the precordium, with varying shapes and with varying degrees of extension to the left. While some degree of delay in the excitation of the right ventricular free wall is frequently noted, this is not always the case. The abnormal findings are constant and they are associated with a normal morphologic and functional status of the heart. The abnormal electrocardiographic finding may be misinterpreted as evidence for acute myocardial injury.

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Gout Simulating Cardiac Pain*

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CHEST pain is a symptom of several disorders related to organs of the chest, the chest wall itself or the abdomen. The recognition of the cause of chest pain and the differential diagnosis of that simulating coronary disease may present considerable difficulty. In the present study the authors wish to draw attention to attacks of chest pain of noncardiac origin which may occur in patients with gout, and are often erroneously diagnosed as "angina pectoris" or "myocardial infarction." Chest pain simulating cardiac pain is not mentioned among the symptoms of gout in current medical books and monographs on gout, and gout is usually not considered in the differential diagnosis of cardiac pain.

To our knowledge, the first to describe chest pain simulating angina pectoris in a patient with gouty arthritis was Libman[1] in 1934. After having suffered from "angina pectoris" for a number of years, the patient was cured by a dietary regimen for the treatment of gout. Referring to Libman's case, Miller[2] in his comprehensive monograph on angina pectoris mentions gout in the differential diagnosis of cardiac pain.

In recent years various investigators have tried to establish a relationship between hyperuricemia and coronary disease[3,4] and have pointed out the advisability of administering probenecid as prophylactic treatment for coronary disease in hyperuricemic individuals.[5] The possibility that Dicumarol might have a beneficial effect through its uricosuric action in the treatment of coronary disease has been considered.[6,7] A significant incidence of coronary heart disease,[8,9] an increased "atherogenic" lipoprotein index[8] and uric acid deposits in the intima of sclerotic coronary arteries[10] have been reported in patients with gout.

Therefore, while these studies may indicate a tendency for coronary heart disease to develop in patients with hyperuricemia and gout, it should be emphasized that patients with gout frequently complain of chest pain which is not of cardiac origin. Recognition of noncardiac chest pain in patients with gout and its differentiation from pain due to coronary disease is important because it implies different prognosis and therapy. Furthermore, knowledge and recognition of this symptom may well reduce the high incidence of coronary disease in patients with gout.

CLINICAL OBSERVATIONS

In our series of thirty-two patients with primary gout, all had a definite clinical and laboratory diagnosis (hyperuricemia on one or more occasions), seventeen complained of chest pain, two of them in their past history only and fifteen while under observation. Eight of these patients were admitted to other hospitals or to our department because of chest pain while nine were sent because of gouty arthritis or uric acid kidney stones. Three of the seventeen patients had myocardial infarction on admission and two had angina pectoris.

Twelve of these seventeen patients with gout had no evidence of coronary disease and their chest pain was diagnosed as being a symptom of gout and not related to the heart. In seven of these twelve patients suffering from noncardiac chest pain, angina pectoris or myocardial infarction had been diagnosed previously in various medical departments including our own.

Character of Chest Pain: By securing an accurate history and carefully observing these patients a varying clinical picture was revealed. The patients had attacks of severe pain in the anterior area of the chest, mostly in the precordium but sometimes on the right, frequently located over a large surface, rarely limited to a small region and in no case radiating to the shoulders, arms, throat, jaws or back. The

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pain was knifelike, rarely dull, superficial, not constricting, pressing, cramping or burning, and not accompanied by fear, sweating or weakness. In most instances the pain had a gradual *onset*, slowly increasing in intensity and reaching a climax after a few hours. Only in some instances was the onset sudden, but it did at times awaken the patient at night. The *duration* of pain varied, lasting from a few minutes to a few days, even as long as five days in one patient. The *intensity* of the pain often varied during an attack, sometimes waxing and waning. The pain generally was not influenced by respiration (except in one case) or by position. Only one patient was more comfortable when lying on his right side.

None of the patients could relate the pain to exertion, excitement, exposure to cold or ingestion of a meal. In three patients, the attack appeared one to three days after a period of excessive eating and drinking. In none did the pain disappear after a short rest nor was it relieved by the administration of nitroglycerin. It could not be ascertained whether salicylates taken at home were effective. The pain in all patients not treated by colchicine terminated gradually, never suddenly. Effectiveness of treatment with colchicine is characteristic and diagnostic.

The first attack of chest pain coincided with the first attack of gouty arthritis in four patients. In the others the arthritis had preceded the first attack of chest pain by periods varying from two to twenty-two years. None of the patients thus far observed remembered having had attacks of chest pain before the appearance of gouty arthritis.

Physical Findings: Examination of the patients during or after the attacks of chest pain was nonrevealing, except for the association with acute arthritis or tophi (four patients) and, in five patients, tenderness of the chest at the location of the pain. Three patients had tenderness of the costosternal junction of one or more left ribs and one patient of a right rib. Only in one patient were there tender circumscribed swellings of the costosternal and sternoclavicular junctions which disappeared a few days after the termination of the pain. In this patient the attack was associated with a rise of temperature to 39°c. while in all others the temperature remained normal or subfebrile. The pain was not accompanied by tachycardia or fall in blood pressure.

Laboratory Findings: The electrocardiogram was normal in eleven of the twelve patients both during and after the attack. Only one had a positive Master's tolerance test. In two patients the levels of serum transaminase was found normal during the attack. All twelve patients had hyperuricemia on one or more occasions, ranging from 5.8 to 12.5 mg. per cent (upper limit of normal in our laboratory is 5.4 mg. per cent). The attacks generally were not associated with an additional rise of serum uric acid, nor could the severity, duration or frequency of the chest pain be correlated with levels of serum uric acid. The serum cholesterol varied from 175 to 250 mg. per cent in eleven patients and only in one did it reach 333 mg. per cent.

Effect of Therapy: Treatment of the acute attack of chest pain with colchicine (dosage as in gout) was effective in all six patients to whom it was administered, the pain disappearing within four to twenty-four hours. Prolonged treatment with probenecid prevented further attacks in five patients in whom the follow-up period was sufficiently long for evaluation.

Case Reports

Case 1. A forty-eight year old male office worker was admitted to the Medical Department on April 3, 1956 with an attack of severe pain, swelling and redness of the metatarsal-phalangeal joint of his right great toe. In the past he had suffered from three similar attacks, each lasting for one to two weeks, the first of which occurred in 1946. He had no tophi or deformation of the joint. Roentgen examination of the hands and feet revealed nothing abnormal. His level of serum uric acid was 6.7 mg. per cent. Treatment with colchicine had to be interrupted because of diarrhea but the arthritis soon receded after the administration of cortisone. Probenecid was administered but discontinued by the patient after discharge.

Since then, he has been admitted three times to another hospital, twice with the tentative diagnosis of myocardial infarction and once with that of angina pectoris. On these occasions he had severe precordial pain lasting two or three days, but no clinical, laboratory or electrocardiographic confirmation of myocardial infarction was obtained. On each admission he had an attack of gouty arthritis, apparently coinciding with the attack of chest pain, twice in the right toe and once in the right knee. He recollected that treatment with nitroglycerin was of no avail while both the joint pain and chest pain improved with the administration of colchicine. Probenecid had been prescribed but he had neglected to take it. In March 1958, he had an attack of left renal colic and passed a uric acid stone.

He was readmitted to our department on March 18,

1959, with severe knifelike precordial pain which lasted many hours. There was slight tenderness of the third left rib at the chondro-osseal junction but no swelling was noted. He had no fever and the electrocardiogram was normal. The pain was not relieved by the administration of nitroglycerin. He was given colchicine, 6 mg. over a twelve hour period, at the end of which time the pain had disappeared. The level of serum uric acid was 6 mg. per cent. He received probenecid (2 gm. per day), an alkalizing drug and 1 mg. of colchicine twice a week. He has been free from attacks since.

CASE 2. A seventy-two year old lawyer was seen at his home on March 5, 1959, because of precordial pain, acute swelling of the chest wall and a rise in temperature. In 1935 he had experienced an attack of severe pain, redness and swelling of the metatarsal-phalangeal joint of his right great toe following the ingestion of a lavish meal which included large portions of liver and kidney and excessive drinking. In the same year he had had six similar attacks. An elevated level of serum uric acid was found, and he was treated for gout with the administration of Atophan and colchicine. In 1946 he had an attack of severe pain in the left side of the chest, initially diagnosed as due to myocardial infarction. However, this diagnosis was not confirmed. The pain gradually declined in intensity and disappeared after four days.

In February 1959 he again suffered an attack of severe precordial pain, this time after having devoted his vacation to large meals and much alcohol. The next day his temperature rose to 39°c., the pain continued unabated for three days and then declined gradually. The electrocardiogram did not show evidence of myocardial infarction.

At the present examination he had severe pain in both the lower and upper regions of the left side of the chest, accompanied by circumscript swelling of the medial part of the left clavicle, the costosternal junctions of the tenth and eleventh left ribs and the third rib about 10 cm. from the midsternal line. The areas of swelling were red, warm and extremely tender. The pain was aggravated by deep inspiration and did not respond to the administration of nitroglycerin or even to morphine. The electrocardiogram was normal. The level of serum uric acid was 12 mg. per cent; the cholesterol, 243 mg. per cent. After about ten days, while he was being treated with phenylbutazone and salicylates, the pain and areas of swelling gradually disappeared.

COMMENT

The cause of the chest pain in gout is not known. Most likely it is caused by acute inflammation around a deposit of uric acid in the tissues of the chest wall, for instance in the cartilaginous or bony part of the ribs or the costosternal junctions. What triggers the acute inflammation around a deposit of uric acid is not known, as is the case for gouty arthritis in general, there being no certainty that each attack represents additional deposition of uric acid. Objective evidence consistent with an acute inflammatory reaction underlying the chest pain was found in only one patient who showed marked areas of swelling near the costal cartilages at the exact location of his pain.

Differential Diagnosis of Gouty Pain and Coronary Pain: As the marked efficacy of the acute and long term treatment makes a correct diagnosis of this type of chest pain important, it is worth while to summarize the features which differentiate it from pain due to coronary disease such as angina pectoris, the variant form of angina pectoris described by Prinzmetal and associates[11] and myocardial infarction: (1) knifelike type of pain, not constricting or oppressing, sometimes sharply localized, generally not radiating; (2) absence of fear or sweating; (3) pain not related to exertion, cold, excitement or an immediately preceding meal; sometimes the pain is related to periods of excessive eating and drinking; (4) prolonged duration of pain without electrocardiographic changes and without clinical or biochemical evidence of myocardial infarction; (5) episodes often associated with acute attacks of gouty arthritis and hyperuricemia or in patients with a history of gouty arthritis; (6) recurring episodes for many years without the occurrence of myocardial infarction; (7) possible local tenderness with swelling at location of pain rarely present; (8) treatment with nitrites are not effective, while the administration of colchicine is often helpful; prevention by long term treatment with probenecid.

Differentiation from Tietze's Syndrome: Alertness to noncardiac chest pain in gout may be important in the differential diagnosis of Tietze's syndrome. In Tietze's syndrome, however, local swelling of the chest is a constant feature,[12] while it rarely accompanies chest pain caused by gout. Moreover, the swelling and pain of Tietze's syndrome are mostly, although not exclusively, located at the upper ribs and the swelling may persist for weeks, months and even years. Finally, it may be presumed that in Tietze's syndrome the administration of colchicine would not be effective. It is noteworthy, however, that de Haas[13] (quoted by Kayser[12]) found the "serum uric acid levels of the patients with Tietze's syndrome on the high side" and it may be worth while to reconsider

the cause and therapy for pain and swelling of the chest in such patients, in the light of the presently described symptoms of gout.

Summary

Attacks of chest pain of noncardiac origin were not infrequent in the patients with gout and often this condition has been diagnosed erroneously as angina pectoris or myocardial infarction. The pain is related to the chest wall and is probably due to involvement of the cartilaginous or bony parts of the ribs or of the costosternal junctions by the deposits of uric acid.

The pain has distinct clinical features distinguishing it from cardiac pain. It is not relieved by nitrites while it is alleviated by colchicine. The attacks may be prevented by long term treatment with probenecid.

Gout must be considered in the differential diagnosis of chest pain, especially chest pain attributed to coronary disease and Tietze's syndrome.

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Eight-Hourly Prothrombin Responses after Induction Dose of Coumadin (Warfarin) Sodium*

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AS THE EXPERIENCE with bishydroxycoumarin (Dicumarol®) has widened, several drawbacks to its general use have come to light so that now it has, to some extent, been replaced by other anticoagulants, particularly its congener,[1] warfarin (Coumadin®) sodium. One of the disadvantages of Dicumarol is its slowness of action, namely, a delay in the onset of hypoprothrombinemia so that therapeutically effective levels may not be achieved for as long as ninety-six hours following the initial dose. Since the clinical value of an anticoagulant may be considered a reflection of its capabilities in both the early establishment of protective cover as well as its duration, we wished to assess the usefulness of Coumadin with respect to these characteristics.

This report is based upon our experience with Coumadin (warfarin) sodium administered to twenty-five patients requiring anticoagulant therapy.

METHODS AND MATERIAL

Twenty-five patients were admitted to St. Alexis Hospital with the following diagnoses: twenty-two with acute myocardial infarction; two with acute thrombophlebitis and one with cerebral thrombosis. Each was given 75 mg. Coumadin orally after blood was first drawn for initial prothrombin time determinations. The oral route of administration was utilized since our patients were not vomiting and retained drugs given by mouth. Coumadin is extremely soluble in water and appears to be absorbed directly from stomach and intestine.

We wished to determine how soon after the administration of this single priming dose of Coumadin the following occurred: a change in prothrombinemia (as evidenced by a change in prothrombin time), the peak level of hypoprothrombinemia, the time of entry into the therapeutic range and the duration of therapeutic range. We wished to determine, too, the persistence of levels of hypoprothrombinemia which, though elevated, are below the generally accepted therapeutic range, i.e., suboptimal; the persistence of excessive levels of hypoprothrombinemia and incidence of bleeding, and the correlation between these latter two.

In order to accomplish this we conducted prothrombin time determinations every eight hours by the Quick one stage method† during the first ninety-six hours of each patient's hospitalization.

We consider therapeutic hypoprothrombinemia to be one and one-half to two and one-half times the control prothrombin time, i.e., twenty-two to thirty-five seconds with a control time of fifteen seconds.

RESULTS

The pertinent information concerning the twenty-five patients studied is summarized graphically in Figure 1. Analysis of the data revealed the following significant points:

Changes in Prothrombin Time during First Forty Hours: At 8 hours: The prothrombin time (PT) in eleven patients was rising; one was in lower limits of therapeutic range. *At 16 hours:* The PT in twenty-three patients was rising; two were now in therapeutic range; thirteen were now in suboptimal range of 19 to, but not including, 22 seconds. *At 24 hours:* The PT in all twenty-five patients was rising; twenty-one were now in therapeutic range; two patients were in suboptimal range, 20 and 9 seconds, respectively. *At 32 hours:* The PT in twenty-four was now in therapeutic range; in one, no significant change in PT, though rising, was yet apparent. *At 40 hours:* The PT in all twenty-five was now in therapeutic range, including one who had not responded readily earlier. One patient showed a rapid spurt in PT from 25 seconds at 32 hours to 62 seconds at 40 hours when she was given 10 mg. K_1.

† Link-Shapiro modification using Simplastin.®

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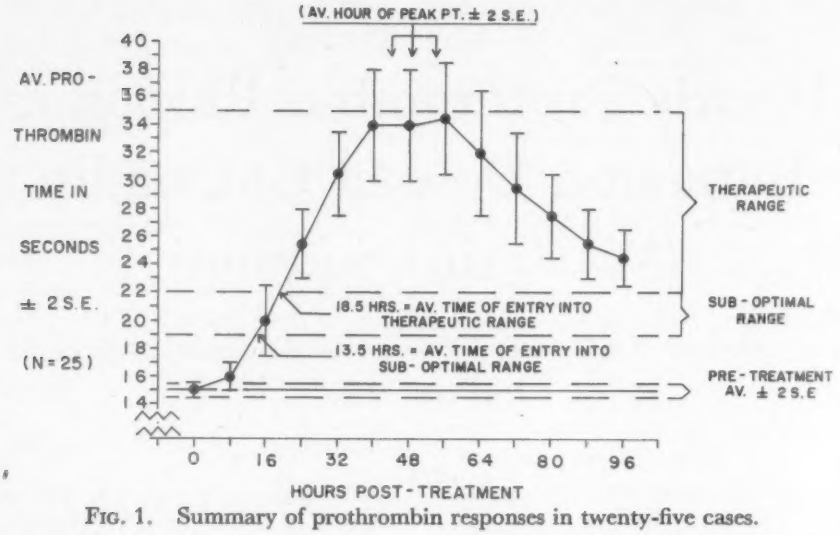

FIG. 1. Summary of prothrombin responses in twenty-five cases.

Peak Level of Prothrombin Time: The time lag between the oral administration of a single priming dose (75 mg.) of Coumadin and the attainment of maximum prothrombin time in each of twenty-five patients was as follows: *At 16 hours*, one patient (45 seconds); *at 24 hours*, one patient (30 seconds); *at 32 hours*, two patients (43 and 44 seconds); *at 40 hours*, eight patients (35, 30, 35, 32, 25, 30, 62, 38 seconds); *at 48 hours*, five patients (30, 29, 34, 28, 36 seconds); *at 56 hours*, six patients (26, 36, 38, 30, 29, 36 seconds); *at 64 hours*, two patients (80, 43 seconds).

Maximum prothrombin time was attained in 76 per cent of patients between 40 and 56 hours. In 16 per cent of patients this maximum was reached in from 16 to 32 hours and in 8 per cent of patients in 64 hours.

Time of Entry into Therapeutic Range: The time lag between the oral administration of a single loading dose (75 mg.) of Coumadin and the entry of each of twenty-five patients into therapeutic range (22 to 35 seconds) was as follows: 8 hours, one patient; 16 hours, one patient; 24 hours, nineteen patients; 32 hours, three patients; 40 hours, one patient.

Twenty-one patients or 84 per cent were in therapeutic range at the end of the first 24 hours following the administration of the initial dose of Coumadin; 96 per cent at 32 hours and 100 per cent at 40 hours.

Duration of Therapeutic Range: The duration of range of therapeutic hypoprothrombinemia in each of twenty-five patients was as follows: 24 hours, one patient; 48 hours, two patients; 56 hours, one patient; 64 hours, two patients; 72 hours, three patients; 80 hours, fourteen patients; 88 hours, one patient; 95 hours, one patient.

In 82 per cent of patients the duration of therapeutic range persisted for 48 to 88 hours; in 4 per cent for 24 hours and in another 4 per cent for 96 hours.

Persistence of Suboptimal Levels: The finding of levels of hypoprothrombinemia which, though elevated, are not within therapeutic range, i.e., suboptimal (19 to, but not including, 22 seconds) was noted in each of the twenty-five patients: *At 16 hours*, thirteen suboptimal; one in therapeutic range (4 per cent); eleven below suboptimal; *at 24 hours*, two suboptimal; twenty-one in therapeutic range (84 per cent); two below suboptimal; *at 32 hours*, twenty-four in therapeutic range (96 per cent); one below suboptimal; *at 40, 48, 56 hours*, all in therapeutic range; *at 64 hours*, one suboptimal; twenty-four in therapeutic range (96 per cent); *at 72 hours*, two suboptimal; twenty-three in therapeutic range (92 per cent); *at 80 hours*, two suboptimal; twenty-two in range (88 per cent); one below suboptimal; *at 88 hours*, four suboptimal; nineteen in range (76 per cent); two below suboptimal; *at 96 hours*, five suboptimal; eighteen in range (72 per cent); two below suboptimal.

Persistence of Excessive Levels: Persistence of excessive levels of hypoprothrombinemia (i.e., over 35 seconds) was noted in seven cases (Table 1).

It is well to note, however, that in five of the patients their highest prothrombin times were 45, 43, 44, 38 and 36 seconds, not excessively high values. In the other two patients the highest levels were 80 and 62 seconds at which points vitamin K_1 was administered with prompt reversal of Coumadin effect on prothrombin depression. In none of these seven patients was there any evidence of bleeding. A correlation between persistently high levels of hypoprothrombinemia and bleeding incidents was not possible.

In order to analyze our data regarding the duration of a therapeutic hypoprothrombinemia more definitively, we took as our first figure the

TABLE I
Persistence of Excessive Prothrombin Time Levels at Hours after Initial Priming Dose of Coumadin

Case	16	24	32	40	48	56	64	72	80	88	96
1	45	39	39	38	40	45	45	38	—	—	—
2	—	—	43	40	40	40	—	—	—	—	—
3	—	—	44	38	—	—	—	—	—	—	—
4	—	45	55	63	72	74	80 (K)	68	57	45	40
5	—	—	—	62 (K)	50	38	—	—	—	—	—
6	—	—	—	38	—	—	—	—	—	—	—
7	—	—	—	—	36	—	—	—	—	—	—

(K) = Vitamin K_1 administered.

test hour when the patient first exhibited therapeutic hypoprothrombinemia and as our second figure the last time a therapeutic range showed plus eight hours (or from onset of therapeutic hypoprothrombinemia to first decline below the therapeutic range). In this manner we found that the duration of therapeutic hypoprothrombinemia was 24 hours in one patient, 48 hours in two patients, 56 hours in one patient, 64 hours in two patients, 72 hours in three patients, 80 hours in fourteen patients, 88 hours in one patient and 96 hours in one patient. In nineteen, or 76 per cent of our patients, then, the therapeutic range lasted for three to four days once it had been attained. In the attainment of therapeutic hypoprothrombinemia and in the decline therefrom, our patients were none the less generally under the protective influence of Coumadin, as evidenced by suboptimal prothrombin times.

One patient (Case 5, Table 1) was given her initial dose of Coumadin for an acute myocardial infarction four days after she had undergone subtotal gastrectomy and gastrojejunostomy for peptic ulcer. The prothrombin test forty hours after the administration of the initial dose of Coumadin was 62 seconds. There was no bleeding. The patient was given 10 mg. vitamin K_1 intramuscularly. There was prompt and gradual recession of prothrombin time to 50, 38, 33 seconds for each of the next three successive eight hour tests.

Another patient (Case 4, Table 1) vomited shortly after she had swallowed her 75 mg. dose of Coumadin. Inadvertently, she was given another 75 mg. Coumadin sixteen hours after the first dose. A prothrombin time of 27 seconds at sixteen hours, i.e., the time of administration of the second 75 mg. dose, indicates probable complete and rapid absorption of the first dose. The prothrombin time of 80 seconds (without bleeding) in the sixty-four hour test was followed by the intramuscular injection of 15 mg. vitamin K_1, and the subsequent rapid and gradual recession of prothrombin time to 68, 57, 45, 40 seconds for each of the next four successive eight hour tests.

COMMENTS

The results of this study indicate that the use of Coumadin provides early onset of therapeutic hypoprothrombinemia (84 per cent of our patients at twenty-four hours). Achievement of therapeutic hypoprothrombinemia (22 to 35 seconds) occurred in an additional 12 per cent at thirty-two hours, and in 4 per cent more at forty hours, so that 100 per cent of our patients were in the therapeutic range at forty hours. Some degree of protective cover (suboptimal range, 19 to 22 seconds, plus therapeutic range, 22 to 35 seconds or higher) was noted in ninety-two to one hundred of our patients from the twenty-four hour through the ninety-six hour test. The duration of the therapeutic range persisted in eighty-two of our patients from forty-eight to eighty-eight after the initial loading dose.

In view of these findings, Coumadin is judged by us an excellent anticoagulant which provides maximal protective cover during the most critical period of disorders requiring effective anticoagulation, that is, the first ninety-six hours following their onset.

SUMMARY

The usefulness of an anticoagulant is predicated upon the speed of initiation of therapeutic hypoprothrombinemia and its duration. We have studied these two components of the response to the administration of a priming dose of Coumadin. Twenty-five patients, selected only as requiring anticoagulant therapy, were each given a single induction dose of 75 mg. Coumadin by mouth. Prothrombin time tests

by the Link-Shapiro modification (using Simplastin) of the one stage method were made every eight hours for the first ninety-six hours following the administration of this dose to each patient, an initial test having been made before treatment with Coumadin was instituted.

By means of this eight hour testing, it was determined that within the first twenty-four hours following the administration of Coumadin, twenty-one patients entered the therapeutic range; three patients, eight hours later; and one patient at the forty hour test. The duration of therapeutic hypoprothrombinemia was forty-eight to eighty-eight hours in twenty-three patients; twenty-four hours in one patient; and ninety-six hours in another. At the twenty-four through the ninety-six hour prothrombin time tests, the great majority of patients (72 to 100 per cent) were in the therapeutic range. There were two instances of excessively extended prothrombin time, without bleeding, which responded promptly to vitamin K_1.

The predictability of action and desirable character of the response to the hypoprothrombinemia-inducing effect of Coumadin are borne out by the objective analysis of the data.

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Bilateral Ligation of the Internal Mammary Artery in the Treatment of Angina Pectoris

Experimental and Clinical Results*

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IN OUR continuing search for a surgical procedure for the alleviation of the effects of coronary artery disease we became aware of the work of Battezzatti, Tagliaferro and De Marchi[1] concerning ligation of the internal mammary arteries in November 1956. The attraction of the operation lay in its technical simplicity, its performance under locally administered anesthesia and the report of subjective improvement in a large percentage of otherwise nonsurgical candidates.[1] So far as could be determined, the only contraindication to surgery was the presence of an acute, unstable myocardial infarction. The rationale and technic of this procedure have been reviewed previously.[1-4] The purpose of the present communication is to report our clinical and experimental experience with the procedure.

EXPERIMENTAL WORK

In an attempt to demonstrate the presence of anatomic and functional collaterals between the pericardiophrenic branch of the internal mammary arteries and the coronary circulation 244 experiments were performed on 175 healthy mongrel dogs. Three major areas of inquiry were explored.

Injection Studies: A description of the method in acute injection studies has been previously published.[2] In addition, this procedure was performed post mortem in many animals that died during other experimental studies. Although there is consistent demonstration of anatomic connection in various degrees, we have no evidence to show that the number and extent of these connections is influenced by ligation of the internal mammary arteries in normal dogs or in survivors of experimentally produced infarction.

A total of twenty-five animals were subjected to acute injection studies. In seven, following the usual precautions, the distal trunks of the internal mammary arteries were injected in the same fashion as had previously been followed for the proximal trunks. Generally this type of injection was almost as efficient in staining the pericardium and appearing in the coronary sinus by way of branches from the superior phrenic artery as proximal injections were by way of the pericardiophrenic artery.

This phenomenon was interpreted as showing that, in accordance with the ligation studies of Holman, using other vessels, the increased volume flow through the pericardiophrenic arteries resulting from ligation of the internal mammary arteries would find a low pressure system distally, encouraging flow. The limited coronary communications with the internal mammary arterial system presumably benefit from this circumstance.

Survival Studies: Seventy-five dogs were subjected to ligation of the anterior descending branch of the left coronary artery. Three groups were studied (Table 1). Fifty-one had bilateral ligation of the internal mammary artery fifteen minutes to twenty-seven days prior to challenge, fifteen had no preparation (controls) and nine had had a Vineberg

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TABLE I

Survival after Ligation of the Anterior Descending Branch of the Left Coronary Artery

Procedure	Interval after Coronary Ligation	No. of Animals	Died in 24 hr.		Survived	
			No.	%	No.	%
Bilateral ligation of the internal mammary artery	Less than 1 hr.	16	10	(63)	6	(37)
	24 to 48 hr.	18	10	(56)	8	(44)
	7 to 27 days	17	9	(53)	8	(47)
	Total.....	51	29	(57)	22	(43)
Vineberg	5 to 8 weeks	9	3	(33)	6	(67)
Control		15	13	(86.7)	2	(13.3)

procedure[6] five to eight weeks previously. Due to technical errors such as ligation of the septal coronary artery branch or death from operative complications or intercurrent infection, twenty-one additional dogs were excluded from evaluation.

Postmortem injection studies of the dogs that died immediately or in the first twenty-four hours were equivocal. There was no apparent increase in collateral flow in the animals with previous bilateral ligation of the internal mammary artery. The Vineberg arterial implants were all open at the time of death and, despite the comparatively short length of time, there were demonstrable mammary-coronary anastomoses. It is to be noted that most of the animals prepared by internal mammary artery ligation prior to the production of coronary occlusion were so prepared only a few hours whereas those prepared by the Vineberg procedure had had one to two months for collateral anastomoses to develop.

Dye Tracer Studies: The greatest effort of our group was directed toward the application of indicator dilution technics to the qualitative appreciation of flow through pericardiophrenic-coronary anastomoses. After a considerable evaluation period the following preparation was considered useful:

The brachiocephalic trunks were isolated proximal and distal to the origin of the internal mammary arteries, the isolated segment being cannulated through the thyrocervical trunk which was ligated about the catheter. This precaution was followed to avoid injury to the internal mammary and pericardiophrenic arteries of small caliber in the dog. A shunt was introduced between the coronary sinus and jugular vein, being so constructed that the coronary sinus blood was not contaminated by blood from the jugular vein and a cannula could be placed into the coronary sinus through the shunt for sampling purposes. Because of the wide variations of oxygen saturation in the coronary sinus blood, Cardio-green* was used for the indicator. Another sampling cannula was placed in the aorta just distal to the aortic valve to detect either T_{1824} or Cardio-green. A mixture of T_{1824} and Cardio-green or Cardio-green alone was injected by a spring-loaded injector. Pairs of injections were performed in the following circumstances: with the subclavian arteries open, ligated distally or ligated distally and proximally; with the internal mammary arteries open or ligated in the third intercostal space; and with the pericardiophrenic arteries open or ligated near their origin (Fig. 1).

In animals previously operated on with bilateral ligation of the internal mammary artery or Vineberg operations, with or without challenge by ligation of the anterior descending branch of the left coronary, injections were made into the aorta proximal to the brachiocephalic trunks.

Only in those animals prepared one or more months previously by the Vineberg operation was the indicator detected in the coronary sinus prior to the aortic sampling cannula, demonstrating that the indicator had reached the coronary sinus by way of coronary anastomoses with the implanted internal mammary artery. In the remaining animals the results were either completely negative or equivocal due to contamination of the coronary circulation by retrograde passage of the indicator as a result of the force of the injection. This latter objection was easily detected by the aortic sampling cannula and identified as such (Fig. 2).

The conclusions reached from these studies are similar to those reported by other investigators.[7–9] There is no evidence of increased extracoronary collateral flow in the first month following bilateral ligation of the internal mammary artery with or without myocardial infarction, nor is there evidence of protection against the effects of ligation of the anterior descending branch of the left coronary artery.

* Manufactured by Hynson, Westcott & Dunning, Inc.

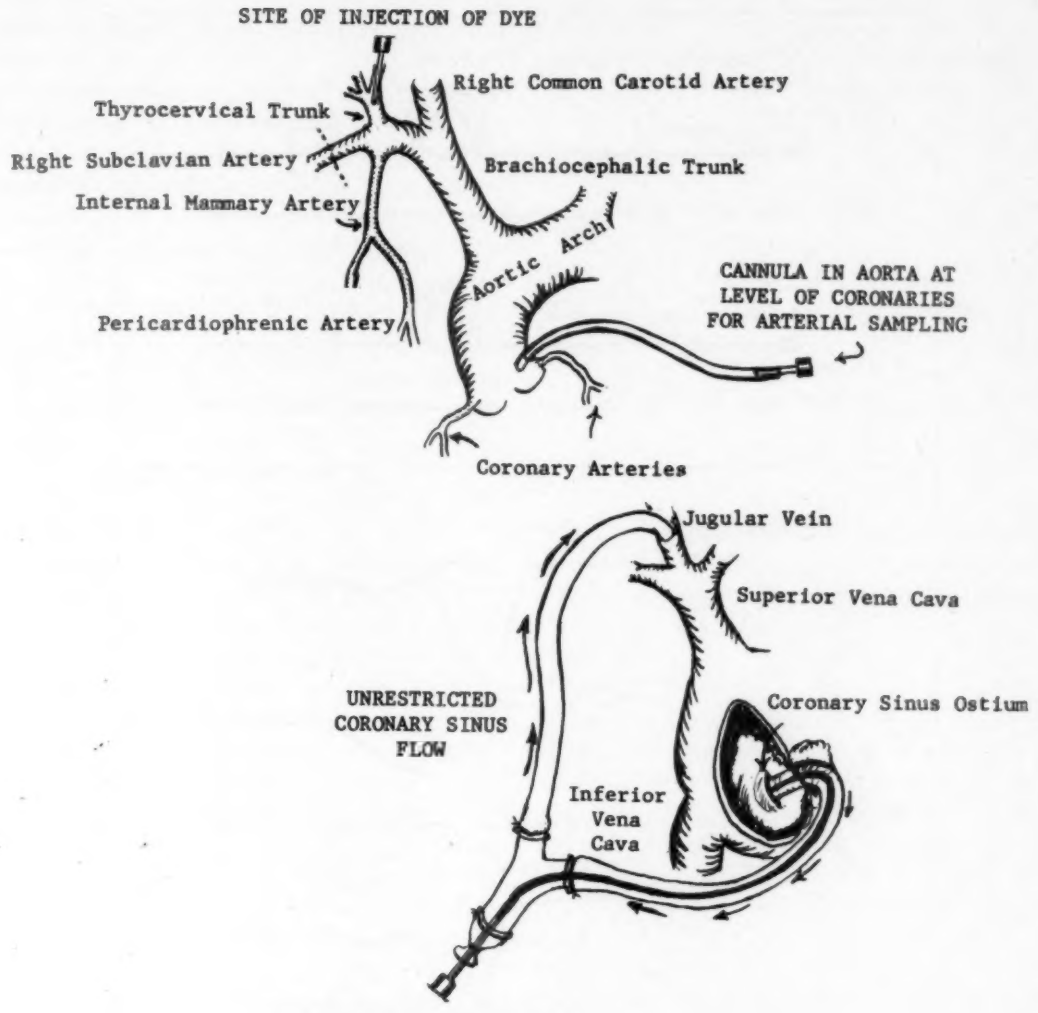

FIG. 1. One method used for cannulation of the arterial and coronary sinus systems for sampling of blood-dye mixture in order to detect the appearance of indicator substance in the coronary drainage prior to the appearance of dye at the origin of the coronaries themselves. It was theorized that if such an indicator could be identified in the coronary sinus before it could be detected in the proximal aorta this would constitute evidence of extracoronary collateral blood supply since the indicator injection was made in the proximal arterial circulation (*top*). In order to sample coronary sinus blood without obstructing coronary sinus drainage and thus impairing coronary circulation, a double cannula system was devised, whereby a large cannula was introduced into the coronary sinus, which was then tied around the cannula so that all its drainage was necessarily conducted out through this tube (*bottom*). It was returned to the venous circulation by inserting a second cannula in the jugular vein and sampling was accomplished with a small polyethylene tube in the coronary sinus cannula proper.

The only favorable results to come to our attention are in more chronic experiments. Zintel,[11] using cardiopulmonary bypass with the aorta clamped, demonstrated an increased coronary circulation six months after bilateral internal mammary artery ligation but no change with acute clamping of the internal mammary arteries. Battezzati et al.[4] presented data concerned with survival, potassium-citrate injections, heart chamber and systemic pressures and coronary flow studies. Garamella and associates,[12] using stockyard pigs, employed an ingenious method of producing acute coronary artery occlusion in the closed chest. Acute ligation of the internal mammary artery gave no protection. Chronic ligation of the internal mammary artery with occlusion performed fifty-eight to sixty-nine days later than the ligation gave a 33.3 per cent survival. The Beck I operation performed with occlusion

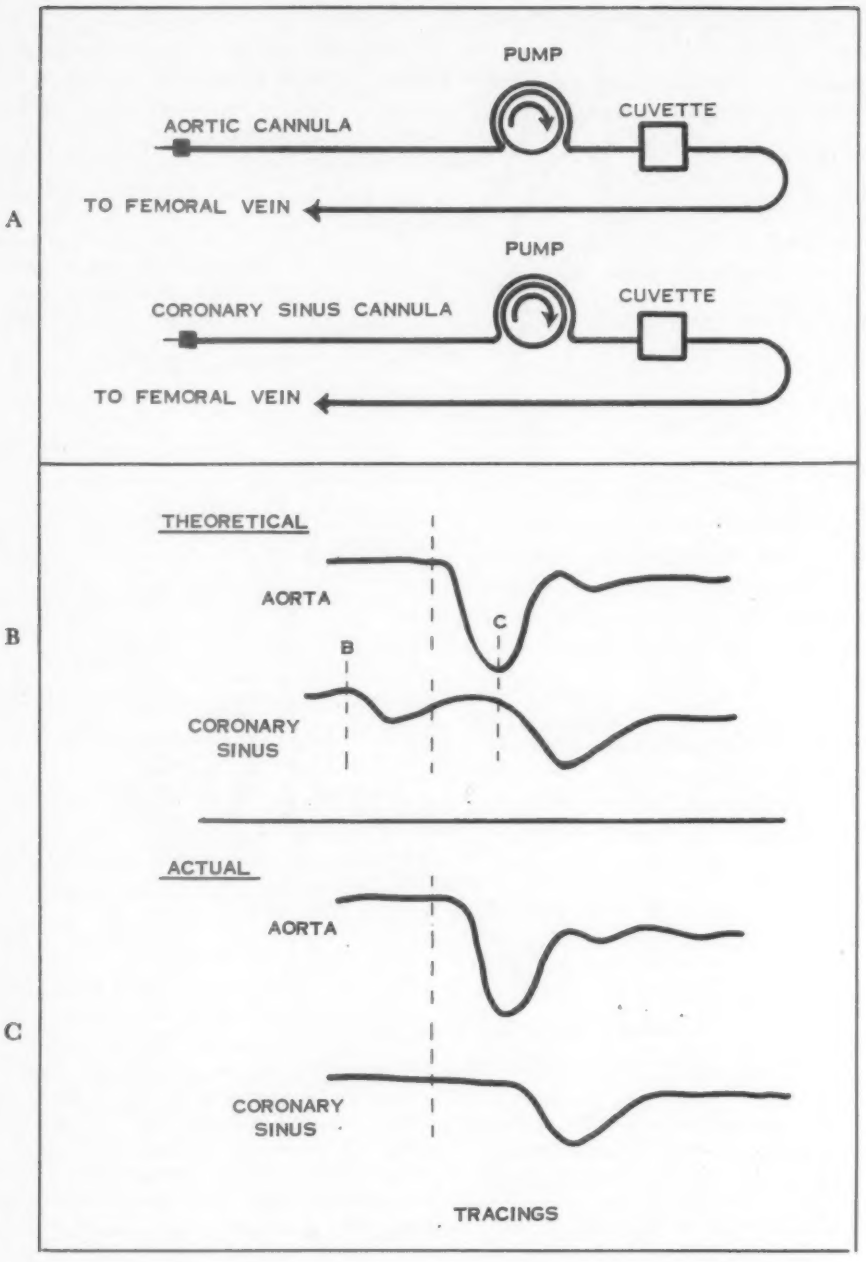

FIG. 2. Detecting system used with the cannulation described in Figure 1. A, two separate Colson densitometers were connected so that the first was fed from the aortic cannula by a constant flow peristaltic pump and the second was fed from the sampling cannula in the coronary sinus by a similar pump. The flow of the sampling pump was adjusted so that it was identical in both systems. The blood from both systems was then returned to a single femoral vein via a wide connection and a small cannula. In this manner continuous sampling could be performed in heparinized animals. B, theoretical tracings. In the case of the coronary sinus cannula, if indicator substance reached the myocardium via extracoronary collaterals arising from the proximal aorta, one would expect the dye to appear in the sampled blood prior to its appearance from the blood sampled at the ascending aorta. C, diagrammed tracings of the types of curves actually obtained in these experiments. As can be seen, no dye was evident in the coronary sinus sample. This would indicate that either there is no coronary collateral blood supply or the amount of dye reaching the coronary sinus before the entire circuit is completed is so small that it cannot be detected. In some of the experiments curves not unlike the theoretical ones diagrammed here were obtained; however, after considerable investigation it was found that the appearance of dye in the coronary sinus prior to the appearance of the major arterial curve was due to backward flow from the injected site which caused the pick-up in small amounts by the coronary circulation of indicator substance. In most of the experiments in which this type of backward flow occurred a small hump was also visible on the arterial curve prior to the appearance of the major deflection.

fifty-two to one hundred two days later gave 27.7 per cent protection.

At the present time a group of animals have been prepared by bilateral ligation of the internal mammary arteries and the experimental production of coronary occlusion is awaited after six months to a year have passed. These results will be available at a later date. It is difficult to assess the contribution of bilateral ligation of the internal mammary artery to changes in pressure and retrograde flow since these measurements are increased in animals that survive acute coronary occlusion.[10]

TABLE II

Results of Bilateral Ligation of the Internal Mammary Artery in 219 Patients Twelve to Thirty Months Postoperatively

Degree of Improvement	No. of Patients	Per cent of Total
Marked	55	25 } 63
Moderate	46	21 }
Slight	38	17 }
No change	38	17
Dead	42	20
Total.....	219	100

CLINICAL EXPERIENCE

SELECTION OF PATIENTS

Bilateral ligation and division of the internal mammary artery has been performed on 239 patients, of whom 219 have been followed up twelve to thirty months postoperatively. There were 172 men and forty-seven women, a ratio of 3.66:1. The age distribution follows the predicted curve with peak incidence in the sixth decade. Of the 219 patients the chief complaint in 212 was the presence of anginal pain. In forty-three patients symptoms had been present less than one year; in fifty-eight one to three years; in thirty-three three to five years; and in seventy-eight over five years. Surprisingly, 115 patients or 54 per cent of this group had angina decubitus. Of the seven patients without angina, four had repeated episodes of pulmonary edema and three had episodes of serious arrhythmias.

At the time of admission 119 patients had unequivocal electrocardiographic evidence of old or recent myocardial infarction. A total of 181 such infarctions were noted, an incidence of 1.5 per patient. Of the remaining 100 patients, seventy-three had definite electrocardiographic evidence of myocardial ischemia and/or damage, or a distinctly positive "standardized exercise test."[13] Ten of the remaining twenty-seven patients had previous tracings of myocardial ischemia or infarction, or severe pain which developed during the standard exercise test without electrocardiographic changes. Seventeen patients, or 8 per cent, had only had angina without objective evidence of coronary artery disease.

Thirty-three patients, or 15 per cent, with angina pectoris and electrocardiographic evidence of coronary artery disease demonstrated radiologically gastrointestinal or biliary tract disease. Three patients had evidence of active duodenal ulceration, three patients had silent cholelithiasis and twenty-seven had a tiny hiatus hernia and/or duodenal scarring.

CLINICAL RESULTS

At the time of this writing, 219 patients have been followed up for twelve to thirty months postoperatively. The evaluation of the results has necessarily been subjective. In the initial phase of this study the patients appeared to fall naturally into specific etiologic categories such as arteriosclerotic, hypertensive and hemodynamic (secondary to aortic valve disease). As the study progressed it was seen that this was an artificial distinction, both clinically and at postmortem, hence the patients have not been arbitrarily divided into such grouping. The postoperative ballistocardiographic and electrocardiographic findings originally were relied upon for proper evaluation of the degree of myocardial improvement or deterioration but little credence was given these changes after the first year in view of the great alterations which may occur regardless of the subjective state of the patient.

Although a number of patients have been followed up by one of us (J. R. K.), the major part of the study has been based on the patient's evaluation of his postoperative condition. For the first year, a questionnaire was submitted at monthly intervals and thereafter at six-month intervals. The patient was asked to relate medications, types and amounts; pain, severity and number of attacks; exercise tolerance, whether or not he was working and in what capacity; and his personal evaluation of status as compared with his preoperative level. If he was asymptomatic, able to work productively,

TABLE III
Site of Infarctions Electrocardiographically Apparent at Time of Admission (119 Patients)

Postoperative Evaluation of Improvement	No. of Patients	Anterior		Posterior		Septal		No. of Infarcts	No. of Infarcts per Patient
		Old	Recent	Old	Recent	Old	Recent		
Marked	30	8	3	19	0	9	2	41	1.37
Moderate	21	5	4	15	0	3	2	29	1.38
Slight	22	9	4	8	1	12	0	34	1.54
No change	17	3	4	12	1	7	3	30	1.76
Dead	29	14	4	13	0	14	2	47	1.7
Total.....	119	39	19	67	2	45	9	181	1.5

TABLE IV
Patients with No Electrocardiographic Evidence of Infarction on Admission (100 Patients)

Postoperative Evaluation of Improvement	No. of Patients	Non-specific ECG Abnormality	Abnormal Exercise Test or Previous Infarct with Normal ECG	Presence of Angina Only
Marked	25	16	1	8
Moderate	25	16	3	6
Slight	16	11	3	2
No change	21	19	2	0
Dead	13	11	1	1
Total...	100	73	10	17

TABLE V
Relation of Result to Occurrence of Angina Decubitus

Postoperative Evaluation of Improvement	No. of Patients with Angina	No. of Patients with Angina Decubitus	Per cent
Marked	52	23	44
Moderate	43	18	42
Slight	38	19	50
No change	38	26	68
Dead	41	29	71
Total.....	212	115	54

had little or no limitation of his activities and considered himself markedly improved, he was placed in the *marked improvement* category. Approximately 25 per cent of the total patients fell into this classification (Table II). Those patients who experienced good relief of symptoms but continued to have occasional episodes of pain and a mild diminution of effort tolerance were considered *moderately improved*. Approximately 21 per cent of the patients have been placed in this category. The patients considered *slightly improved* were those in whom the anginal attacks were less frequent and less severe, whose exercise tolerance remained limited, who were forced to consider only sedentary employment, but felt themselves to be significantly better than before surgery. This category was most difficult to evaluate as there were those whose questionnaires revealed little change as well as those who were disappointed that they had not been completely freed from symptoms despite their considerable improvement. Approximately 17 per cent of the patients were in this category. Another 17 per cent experienced no change in symptomatology and 20 per cent have died since operation. There was no apparent influence on the result caused by age or sex distribution.

As might be expected the number of infarcts per patient in the group of 119 patients with electrocardiographically demonstrable infarction at admission decreased from the *dead* and *no change* categories to the *marked improvement* category (Table III). In the same table, the sites of infarction are also noted. Although no distinct or significant relationship was shown, the rise in septal and anterior infarctions from *marked improvement* to *dead* seemed consistent and of interest.

The incidence of patients with angina only and no electrocardiographic abnormality in the 100 patients without evidence of infarction at the time of admission decreased rapidly from *marked* and *moderate improvement* to *no change* and *dead* categories (Table IV). This was also true of patients with complicating gastrointestinal or biliary tract disease.

There was a definite increase in the percentage

TABLE VI
Duration of Angina with Relation to Results

Postoperative Evaluation of Improvement	No. of Patients with Angina	Duration			
		Less than 1 yr.	1 to 3 yr.	3 to 5 yr.	More than 5 yr.
Marked	52	14	7	9	22
Moderate	43	8	12	5	18
Slight	38	8	10	8	12
No change	38	1	14	7	16
Dead	41	12	15	4	10
Total....	212	43	58	33	78

of patients with angina decubitus from *marked* to *dead* categories (Table v).

Table VI shows the correlation of results obtained with the duration of angina. It appeared that those patients able to survive the coronary artery disease as manifested by this symptom are more likely to achieve relief following operation than those whose symptoms were of shorter duration. Unfortunately, our data processing arrangement did not permit evaluation of frequency or severity of anginal attacks so that this impression may be far from valid.

Deaths: Of the forty-two patients who have died, twenty-eight died as a direct result of coronary artery disease, eleven died of other nonrelated causes and in three the cause of death is not known. In the first group nine patients died from myocardial infarction occurring at or within twenty-four hours of operation. Of the remaining nineteen six were free of symptoms, three were moderately improved, seven were slightly improved and three were unchanged prior to death (Table VII). In the second group (Table VIII) four patients died of renal failure, two of pulmonary embolism following genitourinary surgery and one each from lymphosarcoma, peritonitis, cerebral vascular accident, ruptured aortic aneurysm and rheumatic valvular disease. Of these, three were markedly improved, two were moderately improved, one was slightly improved and five were unchanged.

Status of Living Patients: Only twenty-four, or 13.5 per cent, of the living patients have changed in status over the study period. From the *marked improvement* group, two have transferred to *slight improvement* and one each to *no change* and *moderate improvement* in fifteen, twenty-seven, twenty-four and nineteen months, respectively. From the *moderately improved* group three have transferred to *slight improvement* and two to *no change* in six, thirteen, twenty-seven, twelve and three months, respectively. Two patients have gone from *slight* to *no change* after four and nine months.

In the direction of improvement two patients went from *no change* to *slight* and *moderate improve-*

TABLE VII
Results in Nineteen Patients Dying of Coronary Artery Disease More than Twenty-Four Hours Postoperatively

Postoperative Evaluation of Improvement	No. of Patients	Length of Survival Following Surgery (mo.)
Marked	6	2, 3, 3, 4, 10, 11
Moderate	3	5, 5, 6
Slight	7	6, 6, 6, 9, 10, 10, 13
No change	3	2, 5, 12

TABLE VIII
Results in Eleven Patients Dying from Other Causes

Postoperative Evaluation of Improvement	No. of Patients	Length of Survival Following Surgery (mo.)
Marked	3	3, 4, 10
Moderate	2	10, 11
Slight	1	5
No change	5	1, 1, 1, 7, 10

TABLE IX
Changes of Status of Twenty-Four Living Patients

	No. of Patients	No. of Months Prior to Change
Changed to worse state (13 patients):		
Marked to moderate	1	19
Marked to slight	2	15, 27
Marked to unchanged	1	24
Moderate to slight	3	6, 13, 17
Moderate to unchanged	2	3, 12
Slight to unchanged	2	4, 9
Changed to better state (11 patients):		
Unchanged to slight	1	12
Unchanged to moderate	1	12
Slight to moderate	5	6
Slight to marked	1	4
Moderate to marked	5	12
Total.....	24	

ment after one year, one patient went from *slight* to *marked improvement* after four months, five patients went from *slight* to *moderate improvement* after six months and five patients went from *moderate* to *marked improvement* after one year (Table IX).

In general the maintenance of original status has been remarkably stable in a disease of such variable manifestations. The fact that the members of the markedly improved group for the most part denied symptoms from the first postoperative month was initially a matter of considerable concern; the fact that this improvement has been maintained up to thirty months postoperatively is of continuing interest. This is in keeping with the results cited by Battazzatti et al.[14] but at variance with those as noted by Dimond et al.[15]

Summary and Conclusions

I. Experimental Work

1. The existence of collaterals between the pericardiophrenic branch of the internal mammary arteries and the coronary circulation has been repeatedly demonstrated.

2. We have produced no experimental evidence that ligation of the internal mammary arteries has any consistent influence on these collaterals with regard to flow or number.

3. We have demonstrated no crucial experimental evidence that bilateral ligation of the internal mammary artery in the dog protects the heart from the effects of ligation of the anterior descending branch of the left coronary artery.

4. The effect of bilateral ligation of the internal mammary artery upon experimentally produced coronary occlusion when performed many weeks to months prior to infarction needs further study and clarification.

II. Clinical Experiences

1. In 46 per cent of the entire series and 57 per cent of the living patients a moderate to marked improvement has been noted postoperatively.

2. Of the entire series 63 per cent felt slightly to markedly improved; this represents 79 per cent of the living patients.

3. The postoperative status of the patients is remarkably stable, there being only twenty-four patients, or 13.5 per cent, who have changed in the study period from their original one month evaluation. Eleven of these have regressed clinically, usually after one year or more; thirteen have improved after four to six months.

4. There is reason to believe that longevity has not been increased by the operation. However, in extenuation, it should be noted that 20 per cent of the deaths occurred in patients who had a myocardial infarction at the time of surgery or within twenty-four hours of it, and that roughly 25 per cent died of causes other than coronary artery disease. The remaining group of nineteen patients, or less than 10 per cent of the entire series, is certainly not excessive in view of the extensive disease present and their very guarded initial prognosis.

5. We must assume, lacking evidence to the contrary, that the benefit observed following this type of surgery consists solely in relief of anginal pain by a mechanism as yet unknown.

6. It is suggested that the use of this procedure alone be confined to those patients who cannot tolerate more major surgical therapy. Its use as an adjunct to other forms of surgery such as pericardial poudrage or the Beck I procedure may well enhance the total result obtainable.

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Experimental Studies

Ligation of Internal Mammary Arteries as Related to the Coronary Artery Circulation*

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LIGATION of the internal mammary arteries for treatment of angina pectoris and coronary heart disease has been discussed in many publications. Reference to these publications is omitted from this paper. Only our experiments are reported.

Various tests were established in our laboratory to measure the beneficial effect of a drug or a surgical operation upon the coronary artery circulation. These tests are as follows: (1) backflow measurements; (2) electrical fibrillation (mortality) after test artery occlusion; (3) size of infarct after test artery occlusion and (4) the electrical condition of the heart after test artery occlusion. Each of these tests is related to the amount of oxygenated (arterial) blood delivered to an area of ischemic muscle. When the amount of blood to an area of ischemic muscle is increased by therapy, the condition is improved; when it is reduced, the opposite effect is produced. These statements apply to both the human subject and the experimental dog. The effect of ligation of the mammary arteries on these tests has been studied.

METHODS AND RESULTS

BACKFLOW MEASUREMENTS

Method: This test is done as follows: The circumflex artery is ligated at its origin. This artery is cut distal to the ligature. The cut end is cannulated. The blood that escapes is the backflow. It is the blood in the arterial tree of the ligated artery, and is the only blood available to this segment of muscle when its main source of blood supply is occluded. The blood is measured for thirty seconds and is expressed in cubic centimeters per minute. The pressure in the aorta is maintained at a constant level of 100 mm. Hg while the measurement is made. Between determinations the cut end of the artery is perfused from the carotid artery and an interval of five minutes elapses before the next determination is made. There is some variation in successive measurements under the same conditions of the experiment. Because of these variations the average of several successive measurements is taken to represent the backflow. In some experiments there is a tendency for the backflow to increase with successive determinations. Thus, the tenth or twelfth determination may be slightly more than the first and second under the same conditions. These fluctuations may be within the normal range of variations and should be so considered unless a pattern of augmentation is established in most of the experiments.

The internal mammary arteries were ligated at the interspace between either the second and third or the third and fourth costal cartilages.

Results before and after mammary artery occlusion: 1. The internal mammary arteries were dissected free but they were not occluded. Backflow measurements were made to establish the level for normal. The mammary arteries were then occluded by an arterial clamp and measurements were made after occlusion was established. The clamp was removed and measurements were made again after the occlusion was released. These measurements are given in Table I.

2. Backflow determinations were carried out several weeks after mammary artery occlusion. The internal mammary arteries were ligated and measurements made after an interval of time. These are given in Table II.

* From the Claude Beck Cardiovascular Laboratory, the Western Reserve University School of Medicine, Cleveland, Ohio. This work was supported by grants from the U. S. Public Health Service and the Cleveland Area Heart Society.

TABLE I
Backflow Determinations (Acute Experiments)

Acute Experiments	Internal Mammary Arteries		
	Before Occlusion (cc./min.)	Occlusion by Clamp (cc./min.)	Occlusion Released (cc./min.)
1	4.0	4.8	5.6
	4.4	4.8	5.2
	4.8	5.2	5.2
	4.4		
	4.4*	4.9*	5.3*
2	5.2	3.6	4.4
	4.8	5.2	4.4
	4.4	5.2	4.8
	4.2	5.2	
	4.6*	4.8*	4.5*
3	4.0	4.4	5.2
	4.4	4.4	6.4
	4.4	4.8	6.4
	4.2*	4.5*	6.0*
4	4.0	4.4	4.8
	4.8	4.4	4.8
	4.8	4.8	5.2
	4.8		
	4.6*	4.5*	4.9*
5	2.4	2.4	2.4
	2.4	2.4	2.0
	2.4	2.4	2.4
	2.4*	2.4*	2.3*

* Average figures.

TABLE II
Backflow Determinations (Chronic Experiments)

Chronic Experiments	Interval after Mammary Artery Ligation (days)	Backflow Determinations: Average of Several Successive Readings (cc./min.)
1	42	3.1
2	40	4.0
3	47	5.1
4	47	3.1
5	46	6.0
6	49	4.8
7	41	1.6
8	42	3.8
9	49	4.5
10	49	3.0
		Average 3.9

TEST ARTERY OCCLUSION—MORTALITY AND INFARCT SIZE

Method: The descending ramus of the left coronary artery was the test artery for ligation. It was ligated at its origin and no branches were missed. The septal artery was not included in the ligature. The mortality rate was obtained. Death was produced by electrical fibrillation which in turn was produced by the oxygen differential in the muscle. The size of the infarct was determined in the dogs that did not fibrillate. These dogs were killed three to five weeks after occlusion of the test artery. The infarcts were classified as none, small, intermediate and large.

Results: 3. The internal mammary arteries were isolated and ligated without opening the pleural cavities. The test coronary artery was ligated three weeks later. The results in fifteen dogs were as follows: eleven lived, four died. The mortality rate was 27 per cent. The size of the infarct was determined in six specimens. These were classified as none in zero, small in three, intermediate in one and large in two.

A similar series of experiments was done in which the internal mammary arteries were ligated after opening the pleural cavities. The test coronary artery was ligated three weeks later. The results in twenty dogs were as follows: fourteen lived, six died. The mortality rate was 30 per cent. The size of the infarct was determined in thirteen specimens. These were classified as none in zero, small in two, intermediate in four and large in seven.

These two groups consist of thirty-five experiments. Of these twenty-five lived and ten died. The mortality rate was 29 per cent. The size of the infarct in nineteen specimens was classified as small in five (26 per cent), intermediate in five (26 per cent) and large in nine (47 per cent).

4. Sham Ligations. The internal mammary arteries were isolated by surgical dissection. A piece of silk was placed around them but the arteries were not ligated. The test coronary artery was ligated three weeks later. The results in fifteen dogs were as follows: nine lived, six died. The mortality rate was 40 per cent.

5. Anesthesia. Ether anesthesia was given for one hour. Three weeks later the test artery was ligated. The results in fifteen dogs were as follows: nine lived and six died, giving a mortality rate of 40 per cent.

6. Normal Controls. The test artery was ligated. The results in twenty dogs were as follows: nine lived, eleven died, giving a mortality rate of 55 per cent.

7. Ligation of internal mammary arteries in ten dogs followed by test artery ligation at the same operation resulted in seven deaths, or a mortality of 70 per cent.

Analysis of Results

Backflow Measurements:[1] The average backflow in 144 control experiments as determined by Leighninger in our laboratory is 4.2 cc./minute. Seventy-seven additional experiments have been performed in normal dogs since the first sixty-seven were reported.[4] This corrects the measurement for normal backflow to 4.2 cc./minute. Ligation of the internal mammary arteries does not change the backflow in acute experiments (Table 1). After the clamp is removed from the mammary arteries and after patency is restored the measurements remain within the range of normal figures. Measurements in the long term experiments were normal when there was an interval of time between internal mammary ligation and backflow determination.

Mortality Following Test Artery Occlusion: The mortality following ligation of the descending ramus of the left coronary artery as determined in one hundred normal dogs in our laboratory was 70 per cent.[1-3] When these experiments are considered in groups of ten, the mortality ranged from 50 to 90 per cent. Under item 3, the mortality in thirty-five experiments was 29 per cent. This may appear to be a significant reduction in mortality as compared to the figures for normal controls. However, the mortality in groups 5 and 6 is also lower than the mortality in normal controls, and in these experiments the mammary arteries were not ligated. The mortality in these experiments was 49 per cent. The mortality in item 7 is the same as in normal controls, namely, 70 per cent; and in these experiments ligation of the internal mammary arteries preceded ligation of the test coronary artery, both being done at the same operation.

Size of Infarct after Test Artery Occlusion: Analysis of the size of the infarct in dogs that survived test coronary artery ligation follows: Measurements of control experiments were reported by Stanton et al.[5] Fifteen dogs survived test artery ligation in a series of fifty normal controls. The scale for measurement was 0, small, intermediate and large. An infarct was present in each experiment. It was small in four or 26.6 per cent; intermediate in four or 26.6 per cent and large in seven or 46.6 per cent. This analysis for the normal controls is almost identical to results in item 3.

Conclusions and Summary

The relationship between internal mammary artery ligation and the coronary artery circulation was determined by three laboratory tests. Internal mammary artery ligation, both acute and chronic, had no effect upon backflow from a ligated and cut coronary artery. Ligation of the internal mammary arteries had no effect upon mortality following test coronary artery ligation. In the acute experiments there was no reduction in mortality. In the chronic experiments the mortality figures are within the range of experimental variation. Ligation of the internal mammary arteries followed by test coronary artery ligation did not reduce the size of the infarct in those dogs that survived coronary artery ligation.

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Intercoronary Arterial Channels Produced by Chemical Agents*

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Vascular communications between coronary arteries protect the heart when stenosis or occlusion of these arteries takes place. These channels "ration" the available blood and deliver it to ischemic muscle where it is needed most. They have significant protective value. The Beck operation was designed to produce such intercoronary channels.[1-4] One of the methods to produce them consisted of abrasion of the surface of the heart. In some instances abrasion cannot be done because the heart is too irritable. In such cases a substitute method, such as the use of a chemical agent, is desirable. Experiments with various chemical agents are reported here.

Methods and Results

The experiments were done on dogs. The amount of blood delivered to ischemic muscle was measured by the backflow method.[5] It consists of ligation of the circumflex artery at its origin, incision in the artery distal to the ligature and measurement of the blood that escapes from the severed artery.

Group 1: The Beck operation was performed but abrasion of the heart was omitted. The lining of the parietal pericardium was abraded. The surface of the heart between coronary arteries and veins was touched with cotton applicators moistened in fresh aqueous solution of 5 per cent trichloroacetic acid. Asbestos powder was lightly sprinkled on the surface of the heart. The coronary sinus was narrowed by a ligature to a diameter of 3 mm. The pericardial fat was loosely applied as a graft to the surface of the heart. After an interval of twenty-eight to fifty-seven days backflow determinations were made in thirty-two dogs. These ranged from 2.9 to 19.2 cc./minute with an average of 8.5 cc./minute.

Group 2: A similar procedure was carried out as in group 1 except that 1 per cent trichloroacetic acid was used. The interval between operation and backflow determination was fifty-four to fifty-six days. Twelve experiments were performed. The backflow measurements ranged from 3.5 to 11.8 cc./minute with an average of 6.9 cc./minute.

Group 3: An aqueous solution of trichloroacetic acid was injected into the pericardial cavity without opening the pericardium. The interval of time was twenty-two to fifty-five days. A 5 per cent solution was used and the backflow determinations in six dogs were 1.5 cc./minute with 3 cc. of the solution, 4.2 cc./minute with 3 cc., 2.6 cc. /minute with 10 cc., 4.5 cc./minute with 10 cc., 5.7 cc./minute with 10 cc. and 1.6 cc./minute with 10 cc. In three experiments the pericardium was opened and a 5 per cent solution was applied to the heart with moist cotton swabs. The backflow determinations were 2.8, 3.1 and 4.2 cc./minute, respectively. The average backflow in nine experiments was 3.4 cc./minute. One dog died from a compression scar on the heart produced by 10 cc. of 5 per cent solution.

Group 4: The complete operation was performed including abrasion of the epicardium plus the application of 5 per cent trichloroacetic acid. The interval between operation and backflow determinations was twenty-one to seventy-two days and in one dog it was 380 days. The backflow measurements in eleven dogs ranged from 2.4 to 13.2 cc./minute with an average of 6.5 cc./minute. The measurement in the long term experiment was 6.7 cc./minute.

Group 5: A modified Beck operation was performed. The surface of the heart was not abraded. A solution of 10 per cent trichloroacetic acid was applied to the surface of the heart by moistened cotton swabs. The interval was fifty-six to seventy days. Backflow determinations in eight dogs varied from 2.9 to 6.1 cc./minute. The average was 4.3 cc./minute. One dog died at seventy days from a compression scar.

Group 6: The Beck operation was performed and a light application of 5 per cent solution of trichloroacetic acid was made between the surface branches of

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the coronary arteries. These dogs were operated upon a second time thirty-three to sixty-eight days later. The first operation was through the left side of the chest and the second operation was through the right side of the chest, thus approaching both sides of the heart. The pericardium over the right ventricle was opened where it was not densely adherent. Abrasion, trichloroacetic acid and a light application of asbestos powder were applied over accessible areas of the heart from the right side. This procedure was limited by the adhesions to the heart. A period of thirty-four to fifty-eight days elapsed before backflow determinations were made. In ten dogs these varied from 3.0 to 12.2. cc./minute with an average of 7.1 cc./minute.

Group 7: The procedure consisted of the application of 5 per cent trichloroacetic acid to the surface of the heart plus a sprinkling of asbestos powder to the surface of the heart with about 0.3 g. The interval between operation and backflow determinations was thirty-six to forty-eight days. The backflow measurements in nine dogs ranged from 2.7 to 17.1 cc./minute with an average of 7.5 cc./minute.

Group 8: The Beck operation was performed. Ninety-five per cent phenol was applied lightly by cotton applicators to the surface of the heart. An interval of thirty-three to seventy-seven days elapsed before backflow determinations were made. In one dog the interval was 107 days. The backflow determinations in twenty-one dogs varied from 1.8 to 14.0 cc./minute with an average of 6.5 cc./minute. Six dogs died from compression scars; one had a scar but did not die; another had a hematoma over the right ventricle but death did not ensue.

Comments

The range of variation with backflow measurements is considerable. This applied to both the normal controls and also to dogs that were operated upon. The average backflow in 144 normal dogs as measured by Leighninger in our laboratory is 4.2 cc./minute. The average in seventy-two dogs after the Beck I operation (which is the procedure under discussion) is 8.0 cc./minute and in eight dogs one year after operation it was 10.4 cc./minute. The experiments reported here scarcely support definite conclusions. They provide some general ideas which can be used to guide the work.

The experiments in group 1 indicate that a light application of fresh aqueous solution of 5 per cent trichloroacetic acid can replace abrasion of the heart in the Beck operation. Dosage and concentration of acid are important. In the experiments of group 2 the concentration seemed to be too weak and greater concentration of acid is harmful as shown in the experiments in group 3, in which several cubic centimeters of the acid were injected into the pericardial cavity or applied directly to the heart. The backflow measurements following the complete operation together with the application of 5 per cent trichloroacetic acid (group 4) were 2 cc/minute less than those obtained when application of acid replaced abrasion (group 1). On the basis of these experiments it can be seen that the inflammatory reaction can be too severe for optimum results. The experiments in group 5 in which 10 per cent acid was used support this conclusion.

The Beck operation plus the application of 5 per cent trichloroacetic acid was performed through the left side of the chest as in group 4. At a later date a similar, but limited, procedure was carried out through the right side of the chest so that the entire heart was subjected to the operative procedure (group 5). The determinations were slightly greater than in group 4 but were less than in group 1. The authors have considered doing a repeat operation on those human patients who continue to have pain after the Beck operation. On the basis of these experiments a repeat operation is not indicated. The second procedure is limited by the adhesions of the first operation and is technically difficult.

A modified operation (group 7), consisting of use of 5 per cent trichloroacetic acid and asbestos powder, produced favorable results. This modified operation is used on humans when the heart is irritable, when the left ventricle is markedly enlarged and when the heart cannot tolerate manipulation. It is used in the presence of severe damage in the heart. We would avoid operating upon these patients were it not for the fact that they are almost always helped by the operation.

The Beck operation together with the application of phenol to the surface of the heart (group 8) produced backflow measurements somewhat lower than in group 1. The mortality was due to the phenol and dosage was one of the factors here. Harken et al.[6] used 95 per cent phenol experimentally and in humans without deleterious results and intercoronary channels were demonstrated in the injected specimens. The operation was applied by Harken to eighteen humans without mortality and these patients were relieved of anginal pain after operation. Carbolic acid is a severe necrotizing agent. It destroys tissue, produces scars and its use is not recommended.

Conclusions

In the Beck operation a light application of fresh aqueous solution of 5 per cent trichloroacetic acid applied to the surface of the heart can replace abrasion of the surface of the heart and produce similar backflow measurements. The Beck operation with abrasion plus acid does not seem to augment backflow. A light application of this acid in 5 per cent concentration combined with a light application of powdered asbestos may be considered as a modified operation that is useful when the heart is irritable and cannot tolerate the manipulation of a complete operative procedure. Strong concentrations of trichloroacetic acid and carbolic acid are harmful. They produce scar tissue on the heart and this condition is unfavorable for the development of intercoronary communications.

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Review

Hypometabolic Treatment of Heart Disease*

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IT HAS BEEN DEMONSTRATED that angina pectoris due to coronary artery disease,[1-26] congestive heart failure[1,2,3,6,17,22,27] or various arrhythmias[28,45] may be relieved in the euthyroid patient by the judicious reduction of activity of the thyroid gland. Furthermore, disturbances of the heart such as arrhythmias and heart failure due to hyperthyroidism may be corrected by surgical or medical ablation of the thyroid gland.[24,29] There is some question whether thyroid hormone causes its disturbances because of a direct effect upon the heart or whether it indirectly increases the demands on the myocardium by elevating body metabolism.

EFFECTS OF THYROID HORMONE ON THE HEART

Indirect Effects: In hyperthyroidism the work load of the heart is increased because of an elevated body metabolism.[30] Hyperthyroidism causes an increase in the oxygen consumption of the tissues which is satisfied by a corresponding rise in the cardiac output.[31] Paradoxically, even though there is increased oxygen utilization in the tissues, the arteriovenous oxygen difference is actually diminished because of A-V shunts.[31] Therefore, in order to compensate for the elevated metabolism of the tissue, its needs for oxygen and the presence of A-V shunts, the dynamics of the heart are accelerated in thyrotoxicosis. The stroke volume is not increased yet the cardiac output is greater.[32] It is the increase in the heart rate itself which accounts for the augmentation of cardiac output. During sleep the average pulse rate of patients with thyrotoxcosis is increased 53 per cent above normal.[33] The velocity of blood flow through the body is increased.[34] It is believed that the acceleration of the circulation results principally from peripheral arterial shunts.[30] There is increased heat production in the body which necessitates dissipation of the heat from the skin through vasodilatation of the skin capillaries. The blood flow of the skin of the normal individual requires 3 per cent of the cardiac output while, in the hyperthyroid patient, it requires an average of 6 per cent.[30]

The circulatory adjustments of thyrotoxicosis, therefore, impose a heavy burden on the heart. Following increased physical activity, cardiac output, oxygen consumption and blood pressure are all increased in hyperthyroid patients. The adjustments to thyrotoxicosis are wasteful because they require an increased oxygen supply and an increased amount of cardiac work. The normal heart is able to meet the added stresses produced by hyperthyroidism; but if conditions such as coronary arteriosclerosis, valvular disease or cardiac hypertrophy from previous diseases are present, this adjustment may not always be possible.[30]

Direct Effects: In hyperthyroid animals the oxygen consumption of the myocardium is greatly increased.[35] The glycogen in the heart muscle is depleted and the coronary flow is believed to be increased due to a reduction in coronary arterial resistance.[36]

Present evidence indicates that the direct effect of thyroid hormone on the myocardium may not be effective in the absence of the catecholamines.[37] There appears to be a dynamic interrelationship between the thyroid hormones and those of the adrenal medulla and sympathetic nerve endings. The thyroid hormone inhibits the monamine oxidase catalyst required for catecholamine breakdown. The sympathetic nerve endings in the myocardium

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liberate norepinephrine. An excess of thyroid hormone will prevent the breakdown of norepinephrine which is irritating to the myocardium and will induce arrhythmias. It is believed that the hemodynamic and metabolic changes of thyrotoxicosis are not the result of isolated activity of the thyroid hormones but rather are due to the physiologic effects of the catecholamines which are augmented by the thyroid hormones. The effect of norepinephrine and epinephrine on the heart is greatly increased by an increased concentration of thyroid hormones.

An alternative explanation for the high incidence of arrhythmias in hyperthyroidism is that the augmented venous flow rate to the heart stimulates the atrial muscle and produces an ectopic focus.[38] While the frequent occurrence of atrial fibrillation and tachycardia of the paroxysmal type in hyperthyroidism is not completely understood, it is obvious that the increased thyroid hormone causes increased excitability of the myocardium and that this condition disappears following thyroidectomy. Furthermore, Malinow[39] demonstrated experimentally that it was more difficult to produce atrial arrhythmias in animals that were first made hypothyroid.

Action of the Heart in Hypometabolism

In hypometabolism the peripheral blood flow is diminished. There is an approximate linear relationship between the basal metabolism and the peripheral blood flow.[40] The cardiac output is reduced because the oxygen consumption of the tissues is greatly lessened. The capillaries of the skin are deeper so that less heat is dissipated. The circulating blood volume is probably diminished because heat is conserved in myxedema and this demands a reduced peripheral blood flow.[40] Because of the slowing of the peripheral blood stream, there is greater oxygen utilization by the tissues and thus a greater arteriovenous oxygen difference. This reduces the energy expenditure of the heart and, consequently, the cardiac output and the work of the heart in hypothyroidism are diminished. In myxedema the heart is more efficient than normally. Less energy is utilized in exercising than by a normal subject.[42] The pulse rate is slow in myxedema probably because of the diminished venous flow rate.[30]

Pathologic changes have been noted in the myocardium in myxedema.[12] The heart size is often enlarged due to a pericardial effusion. The myocardium may reveal swollen and vacuolated muscle fibers with loss of striation. Paradoxically, angina and heart failure may also be present in the myxedematous patient and be relieved by small doses of thyroid. Ordinary dosage may cause severe, and often fatal, congestive heart failure or angina pectoris.[43]

I^{131} in the Treatment of Angina Pectoris Due to Coronary Sclerosis and Aortic Stenosis

In 1933, Blumgart, Levine, Berlin and their co-workers[1-3] demonstrated that surgical induction of a hypothyroid state may relieve intractable angina pectoris. In 1950, Blumgart et al.[6] demonstrated that induction of hypometabolism by radioactive iodine may also alleviate angina pectoris. Their studies demonstrated that 67 per cent of patients treated had worth while or excellent results.[17] Jaffe et al.[13] reported that 93 per cent of their patients treated with I^{131} had excellent or good results.

In still another unreported series of 102 patients with arteriosclerotic heart disease treated with I^{131} for severe angina, we have noted that eighty-seven patients benefited from radioactive iodine treatment.[46] We have noted equally effective results in patients with angina pectoris due to aortic valvular disease (Case 1).

The technic of treatment is simple. Although I^{131} has a physical half life of eight days, it may take two to three months to lower the metabolism and relieve the angina.

Adverse Effects: There are few adverse effects from this form of treatment. Hemorrhage into the thyroid substance has occurred immediately after treatment in patients who are receiving anticoagulants. Very often a transient hyperthyroidism occurs in the first few days or weeks after treatment with radioiodine.[8,43] This may result in temporarily increased anginal discomfort. For this reason, it has been suggested[8] that the initial dose of radioactive iodine be a small one and the course of treatment be divided so that the patient receives five or six treatments over a period of four weeks. It has also been suggested[22] that the undesirable effect of such a release of excessive thyroid hormone into the circulation may be prevented by treating the patient first with antithyroid drugs. These drugs deplete the gland of stored hormone and larger doses of radiation can then

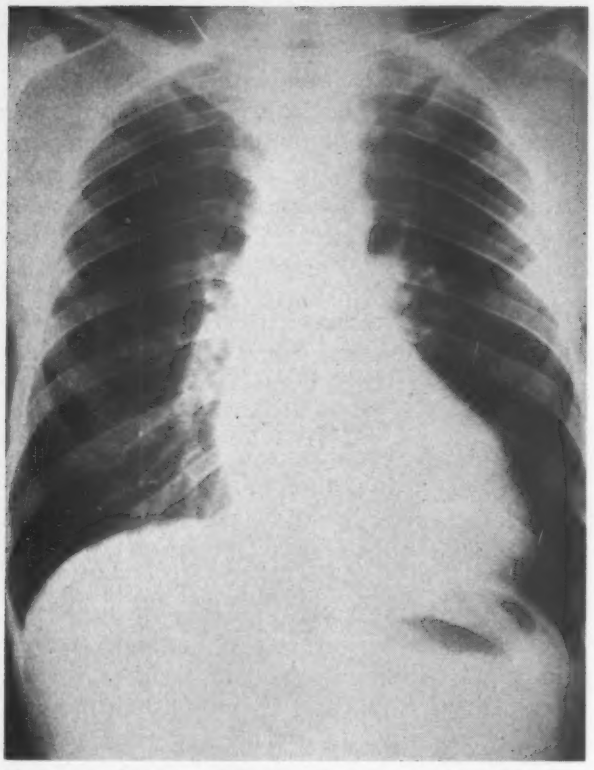

FIG. 1. Case 1. Roentgenogram showing left ventricular enlargement.

be delivered safely to the thyroid gland without danger. In our recent series of ninety-nine patients only two died before the two month course of treatment was completed.

Often in treating patients with radioactive iodine, metabolism may be lowered too much and myxedema results. The annoying symptoms of induced myxedema required treatment with thyroid substance. It is a paradox that the more hypothyroid the patient is, the less thyroid extract he can tolerate. If the metabolism is then elevated too much, the anginal pain again returns. We have found that a dose of 6 to 15 mg. of thyroid a day is usually sufficient to restore the metabolism to a level where the patient again is quite comfortable.

The anginal pain may return in some of the patients a few years after treatment because the thyroid gland regenerated or because of increased coronary artery narrowing. We have administered a second and third course of radioiodine for recurrent angina in subsequent years with equally gratifying results.

Induced Hypometabolism and Serum Cholesterol: One might question whether it is wise to induce hypometabolism in the patient with coronary artery disease for it is well known that the lipid pattern of hypometabolism is usually greatly disturbed, and it is believed by many that the increased serum cholesterol of hypothyroidism may further increase coronary arteriosclerosis. Blumgart[17] has reviewed this problem and demonstrated that the hypothyroid state is not necessarily sufficient to cause the production of atherosclerosis. One thirty-five year old male with rheumatic heart disease treated with radioiodine for congestive failure developed a very high blood cholesterol of between 280 to 400 mg. per 100 ml. for a four year period after radioactive iodine treatment. He died of pneumonia and autopsy demonstrated no narrowing of the coronary vessels. In the future it may be possible to lower the hypercholesteremia induced by I^{131} therapy by the administration of several new thyroid analogs which may have little effect on the heart or body metabolism. We have noted that these substances do reduce blood cholesterol with little disturbing effect on the thyroid sensitive myocardium when used in controlled dosage.[44]

Causes for Relief of Anginal Pain: The induction of a hypometabolic state lessens the frequency of anginal pain and increases the patient's tolerance to exercise mainly because the requirements for cardiac work are minimized following reduction in body metabolism. It is also possible that the patient's pain threshold has been elevated by the treatment so that he does not perceive pain. Other explanations have been offered such as a decrease in sensitivity of the cardiovascular system to adrenergic mediators or an increased rate of development of intercoronary arterial collateral circulation.[17] We have noted an improvement in the personality of many patients following induction of hypometabolism. Cardiologists are well aware of the fact that emotional tension induces angina and thus a lessening of emotions may reduce anginal attacks.

USE OF I^{131} FOR THE TREATMENT OF HEART FAILURE

Blumgart et al.[17] demonstrated that radioactive iodine was beneficial in the treatment of congestive failure in 54 per cent of their patients. We also have noted beneficial effects from this treatment, chiefly in patients with left heart failure due to arteriosclerosis and rheumatic heart disease.

Case 1: This thirty-seven year old dentist complained of precordial distress and episodes of nocturnal

dyspnea. There was a history of rheumatic valvular disease, predominantly aortic stenosis and insufficiency, and mild mitral stenosis since early childhood. He was raised in Madrid, Spain, where he had been practicing. He had recurrent episodes of precordial pain accompanied by attacks of shortness of breath which greatly limited his activities. He had been taking digitalis and nitroglycerin for years. During the month prior to examination, he had experienced six episodes of precordial distress accompanied by dyspnea. These epidoses usually came in the night after he had fallen asleep.

On examination, the cardiac rhythm was normal; the rate was 86 beats per minute. Blood pressure was 146/70 mm. Hg. There were loud systolic and diastolic murmurs at the base of the heart and a diastolic rumble at the apex. A roentgenogram revealed marked enlargement of the left ventricle (Fig. 1). The blood iodine was 5.2 μg. per cent. Radioactive iodine uptake was 27 per cent at twenty-four hours.

Therapy: He was placed at complete bed rest and diuretic therapy was administered twice a week. The attacks of nocturnal dyspnea continued even though he was at rest for three weeks, on a salt-free diet and fully digitalized. These measures having failed, it was decided to lower his metabolism by the administration of 38 mc. of radioactive iodine in divided doses. Following this, the attacks continued for a three month period and then gradually diminished in frequency and intensity. By the fifth month he was completely free of angina and dyspnea and was able to return to full active practice. His physicians report that he has been normally active for the past three years and that he remains free of angina and dyspnea.

Comment: This is a patient with rheumatic heart disease, aortic stenosis and insufficiency and mitral stenosis, who had angina and nocturnal dyspnea which were completely relieved by the administration of radioactive iodine. We have not noted the same degree of success in patients with right heart failure. In many instances of the latter, the failure became more profound following induction of hypothyroidism.

Use of I^{131} for the Treatment of Cardiac Arrhythmias

Recurrent Tachycardias and Atrial Fibrillation

In the euthyroid patient, recurrent tachycardias often occur which are resistant to all forms of preventive therapy. We have demonstrated[28] that paroxysmal atrial fibrillation and tachycardia and ventricular tachycardia may be prevented in the euthyroid patient if the metabolism is lowered with radioactive iodine. In two patients the reduction in metabolism had no effect on premature systoles. We also treated a series of patients with propylthiouracil, but found that such a large dose of this antithyroid drug was required to reduce the metabolism that adverse effects such as agranulocytosis and skin rashes often resulted. In a series of thirty-nine patients treated with radioiodine, the attacks were prevented or markedly reduced in thirty-three but the treatment failed in 6 patients. It usually took three months for the radioactive iodine to reduce the metabolism sufficiently to prevent paroxysms. The metabolism usually had to be lowered significantly for the treatment to be effective. In two instances the attacks recurred unless a myxedematous state was maintained.

It is difficult to understand why lowering metabolism in these patients prevented recurrences of tachycardia because clinical tests such as radioactive iodine uptake, serum protein-bound iodine, basal metabolism and the clinical appearances of the patients indicated that they were not hyperthyroid prior to treatment. Most of our patients had arteriosclerotic heart disease but some had complained of the recurrent attacks of tachycardia since early childhood thirty-five years before the treatment. It is possible that in these patients there was increased liberation of the catecholamines from the sympathetic nerve endings in the myocardium, or a normal amount of thyroid substance in their myocardium was sufficient to prevent the amine oxidase from metabolizing the catecholamines. This would cause an increased irritating catecholamine effect in the myocardium. It is theorized that when the metabolism was lowered, the amine oxidase was not inhibited so that the epinephrine and norepinephrine content of the myocardium was reduced.

Case 2: This patient was a sixty-four year old office worker whose only complaint was that of daily attacks of supraventricular tachycardia. The attacks usually came on when arising in the morning and lasted for about fifteen minutes. They started and stopped abruptly and often caused precordial distress. On examination his blood pressure was 124/86 mm. Hg. The heart sounds were normal and the lungs were clear. He had none of the symptoms or signs of thyrotoxicosis. The electrocardiogram was normal. The chest roentgenogram revealed a heart of normal size and configuration.

Therapy with Propylthiouracil: Attempts were made

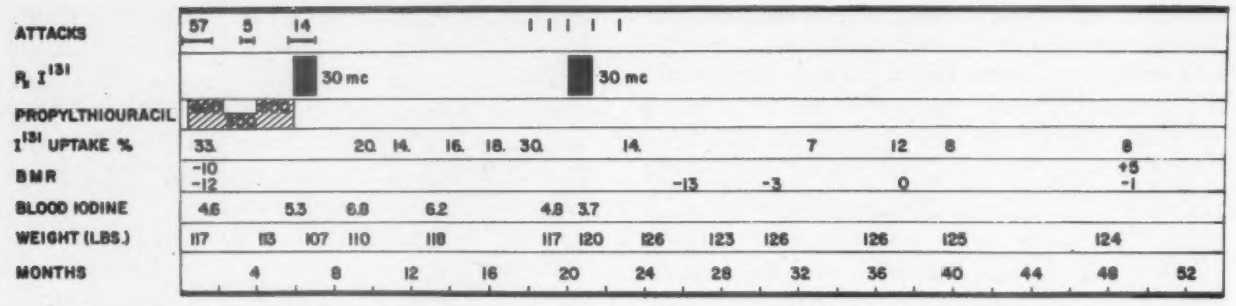

FIG. 2. Case 2. Graph of case history demonstrating effects of therapy with propylthiouracil and radioactive iodine on recurrent attacks of supraventricular tachycardia.

to prevent the episodes of tachycardia first by the administration of quinidine and later with procaine amide, digitalis, rauwolfia derivatives and sedation but the attacks continued. Therefore, he was given 600 mg. of propylthiouracil daily (Fig. 2). At this time his radioactive iodine uptake was 33.4 per cent at twenty-four hours. The basal metabolic rate was −10 and −12 per cent. The blood iodine was 4.6 μg. per cent. The weight was 117 pounds. Ten weeks later the episodes of tachycardia had subsided (Fig. 2). The dose of propylthiouracil was then reduced to 300 mg. a day. Within a three week period the attacks returned every third or fourth day. For this reason the dose of propylthiouracil was again raised to 600 mg. a day. Three weeks later the attacks again subsided and the patient felt completely comfortable. At this time, however, the white blood count dropped to 1,760 per cu. mm. and the propylthiouracil was therefore discontinued. Within a ten day period, the attacks of tachycardia recurred and were as severe as previously.

Radioiodine Therapy: Thirty mc. of radioactive iodine was then administered in divided doses of 5 mc. twice a week. The white blood count returned to normal within a three week period. Within eight weeks the episodes of tachycardia stopped altogether and did not return until approximately one year later. At this time infrequent episodes of tachycardia recurred. The radioactive iodine uptake was now 30.4 per cent, indicating that the thyroid gland had regenerated somewhat. The blood iodine level was 4.8 μg. per cent and the patient's weight was 117 pounds. Because it was believed that thyroid activity had recurred, he was given another 30 mc. of radioactive iodine in divided doses. Following this treatment there have been no attacks of tachycardia for a period of two and one-half years. He complained of a dry skin, coldness and lethargy and was therefore given 6 mg. of thyroid twice a day. This has corrected the symptoms of myxedema and he has not had any return of the tachycardia.

Comment: This is a sixty-four year old man who experienced daily episodes of tachycardia which were prevented by the administration of large doses of propylthiouracil. This drug had to be stopped because it caused leukopenia. Radioactive iodine was then administered and prevented the attacks for a year. However, thyroid activity returned and a few episodes of tachycardia recurred. A second course of radioactive iodine was then given and has resulted in the disappearance of episodes of tachycardia for a further two and one-half year period.

Case 3: The patient, a sixty-two year old woman, complained of frequent attacks of palpitation followed by faintness and chest pain. The episodes started one year previously and were unrelated to physical effort or emotional strain. Within a few minutes of onset, she would experience severe chest pain which radiated down the left arm. She often fainted during these paroxysms. During one typical attack an electrocardiogram revealed ventricular tachycardia (Fig. 3). For about twenty-four hours subsequent to this episode the electrocardiogram, which usually was normal, revealed S-T segment depressions and T wave inversion. An attempt was made to prevent the recurrent episodes of ventricular tachycardia by the administration of quinidine, procaine amide and sedatives. These agents failed and it was decided to lower her metabolism in order to prevent further recurrences of these serious epidoses of ventricular tachycardia. The basal metabolic rate was +4 and +2 per cent; the blood iodine level was 5.4 μg. per cent. The radioactive iodine uptake was 22 per cent at twenty-four hours. The resting electrocardiogram was normal but the Master two-step test was positive. A chest roentgenogram demonstrated a heart of normal shape and size.

Propylthiouracil Therapy: She was given 600 mg. of propylthiouracil a day and within eleven weeks the attacks abated and disappeared completely. When it was noted that suppression of her white count had occurred, the propylthiouracil was stopped. Within a two week period the attacks returned.

Radioiodine Therapy: She was then given 31 mc. of radioactive iodine in divided doses. Nine weeks following the administration of radioactive iodine, the attacks disappeared completely and have not recurred

during the last four years. She complained of coldness, fatigue and increased lacrimation; therefore, she was given 6 mg. of thyroid daily to correct the symptoms of myxedema. The administration of thyroid was continued for a ten month period and then was stopped. Since the small doses of thyroid were administered, she has felt well and has had no complaints for the last four years. The blood iodine is now 4.6 μg. per cent and the basal metabolic rate −6 and −8 %. The radioactive iodine uptake is 18 per cent at 24 hours.

Comment: This is an example of a euthyroid patient with recurrent attacks of ventricular tachycardia which were prevented when the patient's metabolism was lowered first with propylthiouracil and subsequently with radioactive iodine.

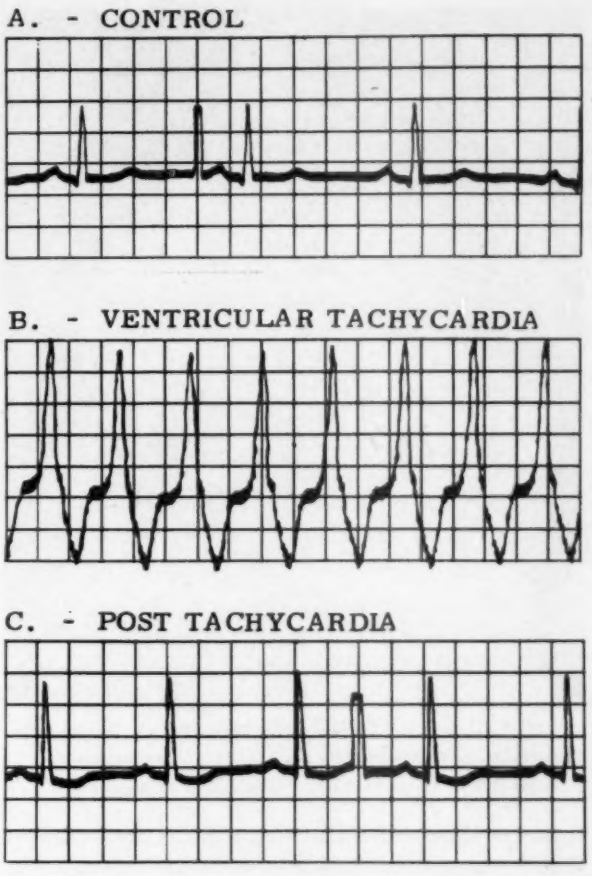

FIG. 3. Case 3. Electrocardiogram (lead II) prior to, during and after episode of ventricular tachycardia.

UNCONTROLLED CHRONIC ATRIAL FIBRILLATION

We have treated eight patients with chronic atrial fibrillation with rapid ventricular rates. In each instance the patient was euthyroid and we could not control the ventricular rate by the administration of digitalis. When the metabolism was lowered in these patients, the ventricular rate was slower and could be readily controlled with small doses of the digitalis glycoside or none at all.

Case 4: The patient, a seventy-seven year old woman, complained of recurrent episodes of dyspnea and precordial pain which radiated into the left arm. The chest pain was brought on when she walked a half block and was usually relieved by nitroglycerin. In the three weeks prior to examination, she had taken 200 tablets of nitroglycerin, 0.4 mg. for the relief of chest pain. In addition, she had been quite dyspneic on exertion and had had a disturbing cough for two months.

Examination revealed a woman who could not lie flat on the examining table because of dyspnea. Her cardiac rhythm was completely irregular; the ventricular rate was 117 per minute. A loud systolic murmur was noted at the apex and there were rales in both lung bases. The liver was enlarged to three fingerbreadths below the costal margin; there was no ankle edema. Because of the gross irregularity of the pulse, it was difficult to record an accurate blood pressure; however, she was not hypertensive

The electrocardiogram revealed auricular fibrillation, ventricular rate 140 per minute (Fig 4). The S-T segments were depressed in leads I and II. The T wave was diphasic or inverted in leads I, II, aVL, aVF and V_2 to V_6. Attempts were made to slow the ventricular rate by increasing the dose of digitalis but this induced disturbing nausea. The patient was unable to tolerate more than 0.25 mg. of gitalin

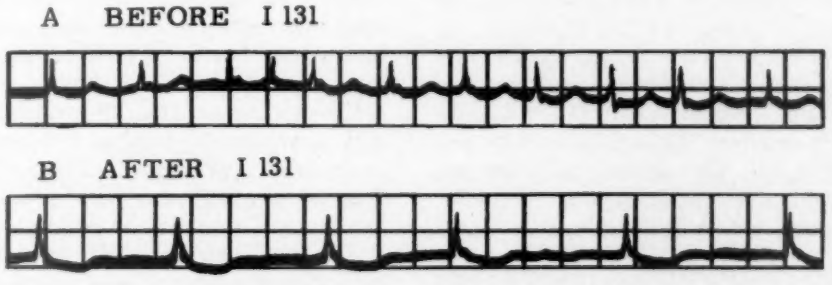

FIG. 4. Case 4. Electrocardiogram showing atrial fibrillation. A, before and B, after radioiodine treatment.

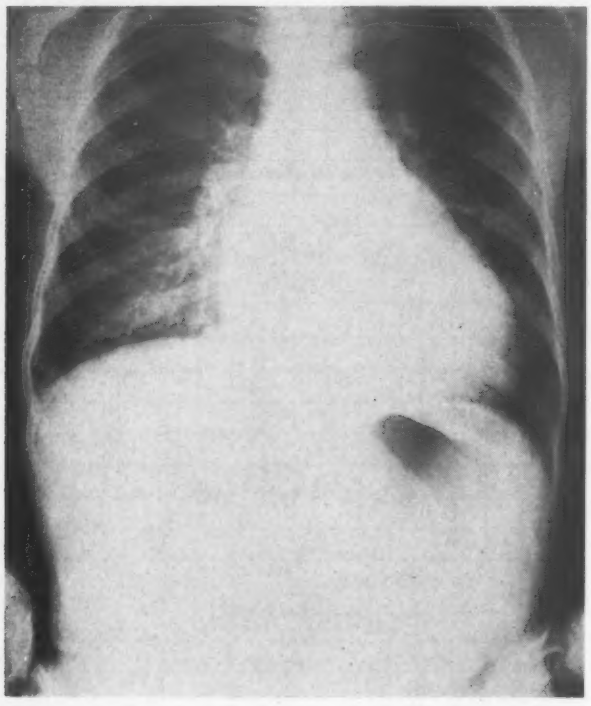

FIG. 5. Case 5. Teleoroentgenogram showing generalized cardiac enlargement.

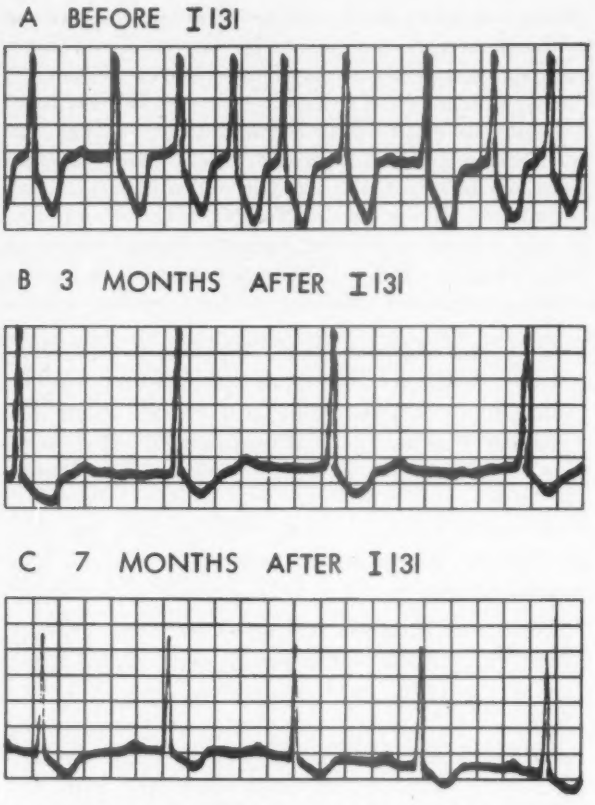

FIG. 6. Electrocardiogram; A, before, B, three months and C, seven months after radioiodine therapy. Note slowing of ventricular rate and subsequent reversion to normal sinus rhythm.

a day. The ventricular rate could not be slowed despite the use of mercurial diuretics, chlorothiazide, salt-free diet and complete bed rest.

Radioiodine Therapy: After six weeks of this intensive treatment, the rapid ventricular rate persisted and the congestive cardiac failure did not improve. The radioactive iodine uptake at this time was 32.6 per cent at twenty four hours; the blood iodine was 6.4 μg. per cent. The patient was then given 29.51 mc. of I^{131} in divided doses over a four week period in an attempt to slow the ventricular rate and prevent the angina.

Within a three month period the radioactive iodine uptake diminished to 1.7 per cent and the patient stated that she did not require as many nitroglycerin tablets for pain. The ventricular rate slowed to about 90 per minute and she no longer required the twice weekly mercurial injections to prevent the dyspnea. Six months later her radioiodine uptake had risen to 32 per cent and she was given a further dose of 12 mc. of I^{131}.

For the next two years after treatment she was completely free of angina and dyspnea and felt very well. The pulse rate remained about 72 per minute and she no longer required digitalis to control the ventricular rate (Fig. 4). The radioactive iodine uptake was 16 per cent. She appeared to be euthyroid except that her eyelids were a little puffy.

Comment: This arteriosclerotic patient had chronic auricular fibrillation with a rapid ventricular rate, angina of effort and congestive heart failure. The ventricular rate could not be slowed because of digitalis sensitivity. When her metabolism was lowered with radioactive iodine, the ventricular rate slowed and the angina and congestive failure disappeared.

Case 5: A sixty-four year old woman, with known rheumatic mitral and aortic valvular disease since the age of nineteen, complained of shortness of breath and palpitation. These symptoms had increased in severity in the four years prior to examination. During this time, the pulse rate was rapid and could not be slowed by digitalis.

Examination showed enlargement of all cardiac chambers (Fig. 5). There was a systolic murmur at the apex and aortic areas and a diastolic murmur at the base of the heart. The blood pressure was 148/60 mm. Hg. The cardiac rhythm was irregular. An electrocardiogram (Fig. 6) revealed atrial fibrillation with a ventricular rate of 114 per minute and left ventricular hypertrophy. The protein-bound iodine was 6.4 μg. per cent; the radioiodine uptake at twenty-four hours was 32 per cent.

Therapy: The ventricular rate could not be slowed with digitalis therapy and attempts to convert the arrhythmia with quinidine failed. Therefore, the patient was given 32 mc. of radioactive iodine in

divided doses. Within a three month period the ventricular rate slowed to 76 per minute and digitalis was discontinued (Fig. 6). This patient has been followed for an additional two year period. The most recent protein-bound iodine level was 4.1 μg. per cent. There have been no recurrences of the rapid arrhythmia. Six months after the radioiodine treatment the rhythm spontaneously converted to sinus rhythm and has remained regular for the last eighteen months. At present there is no evidence of congestive failure and the patient feels well.

Comment: This is a sixty-four year old woman with rheumatic valvular disease and auricular fibrillation with a rapid ventricular rate. Because the rate could not be controlled with digitalis, she was made slightly hypometabolic with radioactive iodine. Following this treatment the ventricular rate slowed, and within a six month period the fibrillation converted spontaneously to regular sinus rhythm.

Blumgart[45] demonstrated that chronic auricular fibrillation was often converted to regular rhythm when euthyroid patients were treated with radioactive iodine. We have also noted this in two of our rheumatic patients with giant atria who had chronic auricular fibrillation for four and seventeen years, respectively. These patients were given radioactive iodine because the ventricular rate could not be controlled with digitalis. When the metabolism was lowered with radioactive iodine, they spontaneously converted to regular sinus rhythm.

Summary

1. The induction of the hypometabolic state with radioactive iodine in the euthyroid patient is often effective in controlling (1) severe angina pectoris due to coronary arteriosclerosis or rheumatic heart disease; (2) congestive heart failure; (3) recurrent tachycardia and (4) uncontrolled chronic auricular fibrillation.

2. Other antithyroid drugs are also effective in the treatment of these conditions but the effective dosage is so large that adverse toxic effects often occur.

Acknowledgment

We would like to thank Messrs. and Mmes. Irving and Normal Feintech, William Forman, Eric Koenig and E. D. Mitchell who gave financial support to this study.

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Report on Therapy

Use of a Long-Acting Quinidine Preparation in the Reversion of Atrial Fibrillation*

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RECENTLY, Bellet et al.[1] reported the study of a long-acting quinidine gluconate preparation compounded in tablet form, with a specially processed hydrogenated vegetable oil base so that the drug may be released gradually. Whereas oral ingestion of a single dose of regular quinidine preparations led to a peak plasma concentration in from one to three hours and negligible amounts at the end of twenty-four hours, the peak concentration after a single oral dose of the long-acting preparation was reached in four and four-fifths hours and plasma quinidine was still present in amounts averaging 1.07 mg./L. after twenty-four hours. This paper gives the results of the use of this long-acting quinidine gluconate preparation in the reversion of atrial fibrillation. Such a preparation would have the advantage of a simple dosage schedule both in therapeutic trials and maintenance medication. In addition, a sustained plasma concentration may be more successful in effecting the reversion of atrial fibrillation than the fluctuating levels found with the use of shorter-acting preparations.

METHODS AND MATERIALS

Patients with electrocardiographically confirmed atrial fibrillation were considered candidates for quinidine reversion. The cause, duration of atrial fibrillation and/or a previously attempted reversion was not considered a contraindication. In addition to initial investigation, including electrocardiographic and roentgenographic examination of the chest, thyrotoxicosis was specifically excluded by determinations of either protein-bound iodine or radioactive iodine uptake.

A total of eighteen patients with atrial fibrillation received the long-acting quinidine gluconate preparation. Fifteen were between the ages of fifty-seven and seventy-seven years, all of whom were found to have arteriosclerotic heart disease with the exception of a sixty-five year old man with luetic aortic insufficiency. Four of the fifteen had complicating hypertension; however, none had evidence of recent myocardial infarction. The three remaining patients were men in the mid-thirties with the valvular lesions of inactive rheumatic heart disease. Two had mitral stenosis predominantly while the third had aortic stenosis only. Because of the small number of patients, no attempt to analyze results in terms of ages or causes was believed justified.

The duration of atrial fibrillation could not be determined in all patients. The range, however, was from two weeks to eight years. Five had had arrhythmia for three months or less, four for two to three years and two for eight years. Thirteen of the eighteen patients had manifestations of congestive heart failure prior to the attempted reversion.

Each patient was fully digitalized before reversion was attempted. In addition to improvement in cardiac decompensation, a ventricular rate of 90 per minute or less was attained in each patient. On the day before long-acting quinidine gluconate therapy was begun, a test dose of quinidine sulfate was given. It should be pointed out that the anhydrous quinidine content is 82.6 per cent of quinidine sulfate and 62.3 per cent of the long-acting preparation.

Dosage: The drug schedule used for attempted reversion was as follows: (1) The initial dosages were 0.6 gm. (two tablets) of the long-acting quinidine gluconate† administered every eight hours for three days, making a total of nine doses. (2) If reversion to sinus rhythm did not take place during this period and no evidence of toxicity was present, the dose was increased to 0.9 gm. administered every eight hours. One exception occurred in the schedule and will be described under "Results."

All patients were followed up by frequent clinical and

† This preparation was supplied by the Wynn Pharmacal Co., Philadelphia, Pennsylvania, as Quinaglute Dura-tabs S.M.

* From the Cardiovascular Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri. This work was aided by a grant from the Wynn Pharmacal Co., Philadelphia, Pennsylvania.

electrocardiographic examinations. Maintenance dosage of quinidine gluconate after reversion was 0.6 gm. administered twice a day.

Results

In all but one of the seventeen patients who received the long-acting quinidine gluconate according to the schedule outlined previously, normal sinus rhythm was ultimately restored. Seven had reverted on or before the third day of therapy; an additional seven had reverted between the fourth and sixth days. Another patient was found to have normal sinus rhythm on the eighth day. In one seventy-two year old man in whom reversion had failed to occur by the ninth day, a staphylococcal abscess necessitated prolonged hospitalization. He was given 0.9 gm. of the long-acting preparation every eight hours, and reverted to normal on the twentieth day. An additional patient to the seventeen reported on herein was a fifty-four year old woman in whom reversion was attempted with quinidine sulfate. After she had received a maximum of 0.6 gm. of quinidine sulfate every two hours for five doses, atrial fibrillation persisted and she was given a maintenance dose of 0.6 gm. of long-acting quinidine gluconate twice a day. One week later sinus rhythm was restored. One of the seventeen patients included in this series also reverted to normal with the long-acting preparation after quinidine sulfate medication had failed.

The one therapeutic failure occurred in a thirty-seven year old man with rheumatic aortic valvular disease in whom runs of ventricular tachycardia developed on the eighth day of therapy. This ventricular arrhythmia represented the only serious toxic effect encountered. One patient developed moderate gastrointestinal symptoms and another complained of tinnitus. In each case the complaint disappeared promptly after successful reversion and reduction of medication to a maintenance dosage. None of the patients who reverted to sinus rhythm displayed electrocardiographic evidence of toxicity.

Because of the small number of patients in this series no comparison with other reports can be made. Our results are encouraging, however, and warrant further use and evaluation of the agent in the termination of atrial fibrillation.

Summary

A specially compounded quinidine gluconate preparation is now available which has been shown by quantitative measurement to attain significantly prolonged therapeutic serum quinidine levels. A clinical study to evaluate specifically the efficacy of this compound in the reversion of atrial fibrillation was performed in eighteen patients with electrocardiographically confirmed atrial fibrillation.

In all but one of the patients the arrythmia was successfully reverted to normal sinus rhythm. In only one patient did evidence of quinidine toxicity develop which necessitated termination of therapy without successful reversion.

It is believed that the results of this series are encouraging and the long-acting quinidine preparation utilized has definite value as an antifibrillatory agent.

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Case Reports

2:1 Bundle Branch Block*

Classification with Special Reference to the Critical Heart Rate

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ALTHOUGH there had been previous reference to 2:1 bundle branch block,[1–3] the first comprehensive and convincing report of this condition was made by Leinbach and White in 1928.[4,5] It is extremely rare and its existence has even been questioned.[6] Only a few cases were found in the literature by Boyer in 1939[7] and by Sandberg et al. in 1951.[8] A form of intermittent bundle branch block, its mechanism may be concerned with critical rate phenomena,[9,10] especially because of the 2:1 pattern. Also, true cardiac alternans or alternation may be involved. It is our purpose to describe a case of 2:1 bundle branch block, the thirteenth such case in the literature and the first with a twelve lead electrocardiogram of this pattern, briefly review the cases previously reported and discuss its mechanism, especially in regard to critical rate.

CASE REPORT

A. B., a sixty-two year old white man was first admitted to Beth Israel Hospital, on May 10, 1957, because of increasing congestive heart failure and pain in the chest. He had had a myocardial infarction two years previous and since that time had been experiencing increasing fatigue, dyspnea on effort, paroxysmal nocturnal dyspnea, orthopnea and edema of the ankles. One week prior to admission these symptoms grew worse and he began to have constricting pain in the chest. He had rarely consulted his physician and digitalis was taken only sporadically.

On physical examination he appeared acutely ill and short of breath. His pulse rate was 96 per minute, respirations 30 per minute; temperature was 99°F. The veins in the neck were markedly distended when the patient was in the sitting position. There was dullness with absent breath sounds at both lung bases and moist rales up to the clavicles. The point of maximal cardiac impulse was at the left anterior axillary line in the sixth intercostal space. The heart rate was regular with sounds of normal intensity. A_2 equalled P_2 and no murmurs were heard. The blood pressure was 124/94 mm. Hg. The liver was palpable 5 cm. below the costal margin and was moderately tender; the spleen was not palpable. There was 4 plus pitting edema of the extremities but no clubbing or cyanosis.

Laboratory Data: There was moderate leukocytosis of 15,800 but the sedimentation rate was normal. The serum transaminase (GOT) was 28 units. The venous pressure in the antecubital vein was 240 mm. saline, rising to 340 mm. on right upper quadrant pressure. The arm-to-tongue circulation time with Decholin® was prolonged to 29 seconds. Teleroentgenogram of the chest revealed a generally enlarged heart and the presence of increased bronchovascular markings and bilateral pleural effusions. The electrocardiogram taken on admission showed changes typical of myocardial infarction of the posterior wall.

Course: The treatment consisted of bed rest, a low sodium diet, Mercuhydrin and small doses of digoxin, 0.25 mg. daily, in view of the unknown state of digitalization. There was a weight loss of 8 pounds on the first hospital day. On the second day, a severe cough developed with hemoptysis and the patient's temperature rose to 102°F. Bilateral tenderness of the calf was present at this time and a positive Homans' sign. Because of suspected pulmonary embolism, the femoral veins were ligated. Anticoagulants were thought contraindicated because of a past history of "stomach ulcer" and "tarry" stools. Right thora-

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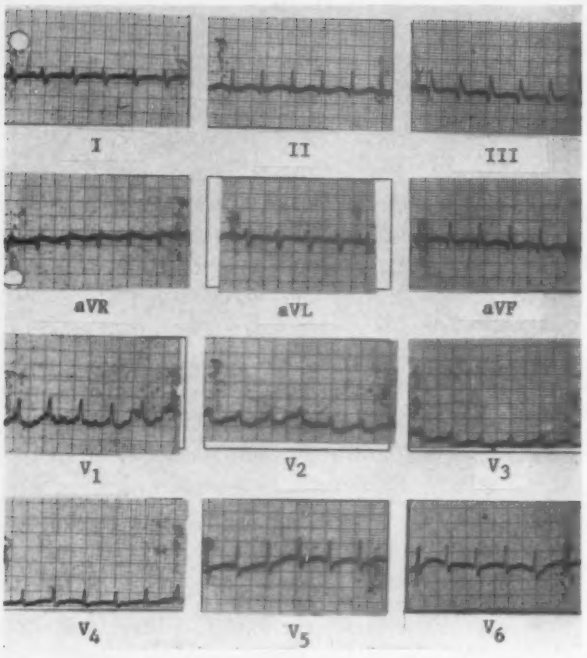

FIG. 1. Electrocardiogram, May 12, 1957, showing complete 1:1 bundle branch block.

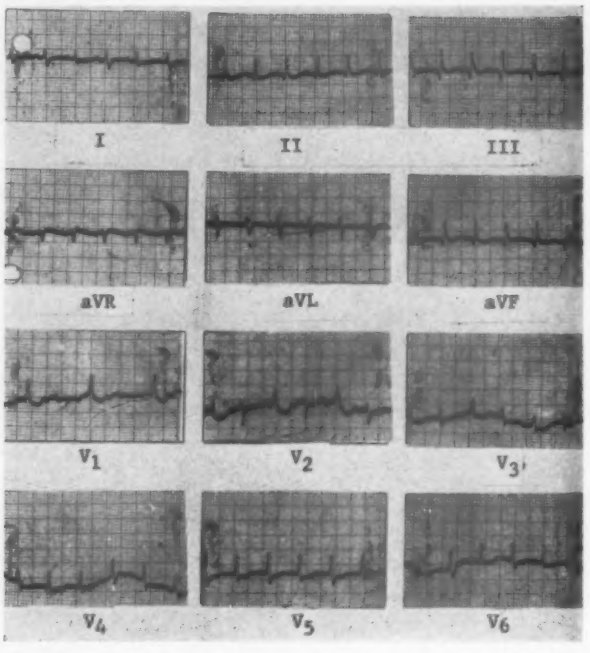

FIG. 2. Electrocardiogram one hour after Figure 1; 2:1 bundle branch block.

centesis was performed and 1,200 cc. of straw colored fluid was removed.

Tachycardia of 144 per minute was noted in the electrocardiogram, with the pattern of right bundle branch block. When the cardiac rate slowed to 139 per minute, the right bundle branch block pattern was present only on alternate beats. Subsequent electrocardiograms, all with cardiac rates of less than 139 per minute, failed to show the right bundle branch block. Despite therapy for congestive heart failure and pulmonary infarction the patient became increasingly dyspneic and cyanotic and died on the seventh hospital day. Permission for an autopsy was not granted.

ELECTROCARDIOGRAMS

The first electrocardiogram was taken on May 10, 1957. There was regular sinus rhythm with a rate of 100. QRS was 0.08 second. Significant Q and negative T waves were present in leads II, III and aVF, the initial 0.04 second frontal QRS vector and the T vector pointing away from the inferior surface of the left ventricle. S waves were absent in lead I, and in V_1 there was an rS. The electrocardiogram obtained on May 11, 1957 showed no significant serial changes. The next day, May 12, the heart rate suddenly increased to 144 per minute and a right bundle branch block pattern appeared in the tracing (Fig. 1). The P waves and P-R intervals were normal. A total of 134 ventricular complexes were recorded in the routine twelve leads. All were of the right bundle branch block pattern. Cycle lengths were 0.405 to 0.42 second (Figs. 1 and 3).

One hour later another electrocardiogram was taken (Fig. 2). The cardiac rate was approximately 140 per minute. The wide QRS complexes of 0.12 second alternated with those of normal width, 0.08 second. A total of 138 ventricular complexes were recorded, all consistent with 2:1 bundle branch block. Cycle lengths were 0.42 to 0.435 second (Fig. 3). At the more rapid heart rate bundle branch block occurred with each beat (1:1) and at the slightly less rapid rate there was 2:1 bundle branch block. The critical cardiac rate was 142, with complete 1:1 bundle branch block* at rates of 148 to 142 per minute and 2:1 block at 142 to 137 beats per minute.

For the period of 2:1 bundle branch block, the length of the cycles immediately preceding the normal beats was compared with the length of the cycles preceding the blocked beats. No significant differences were found. Three tracings were taken later (Fig. 4); the cardiac rates were 100, 107 and 115 per minute, respectively. All QRS complexes were of normal duration, 0.08 second.

REVIEW AND DISCUSSION

Early[6] it was thought that partial bundle branch block analogous to partial A-V block did not occur or was extremely rare. This was because of the small time interval (to 0.04 second) in which increments of bundle branch block could occur, the impulse then arriving from the contralateral side of the

* Complete 1:1 bundle branch block is used to denote total block in a main bundle branch for each of a series of beats; without the 1:1 it refers to the individual beat only, that the QRS interval is 0.12 second or more.

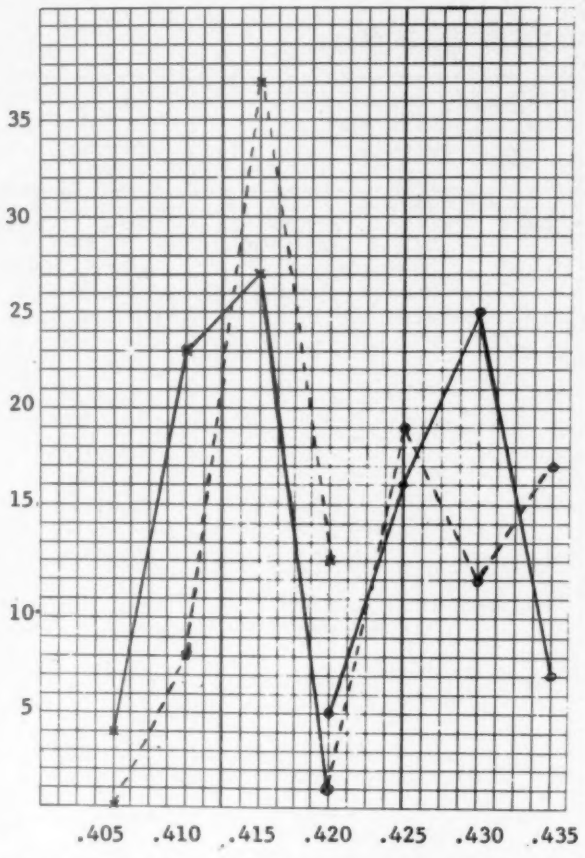

FIG. 3. Variations of the cycle length in complete 1:1 bundle branch block and in 2:1 bundle branch block. Ordinates denote number of cycles, abscissas cycle lengths in seconds. Unbroken line denotes limb leads, broken line precordial leads. Crosses represent observations on the twelve lead electrocardiogram taken on May 12, 1957 (Fig. 1A) with complete bundle branch block 1:1; open circles represent observations on the electrocardiogram taken one hour later (Fig. 2) with 2:1 bundle branch block. Cycle lengths for 1:1 bundle branch block range from 0.405 to 0.420 second, those for 2:1 bundle branch block from 0.420 to 0.435 second.

ventricular septum. In partial A-V block the corresponding interval can be as much as one second, twenty-five times as long.[11] Later, however, instances of 2:1 bundle branch block were observed. In most cases this pattern of block was seen for very brief periods, about fifteen to twenty-five cycles, in response to exercise, vagus pressure or drugs. In a search of the literature we have been able to find only twelve acceptable cases of 2:1 partial bundle branch block with regular sinus rhythm, and in some of these the electrocardiographic illustrations were not wholly satisfactory.[12,13] Earliest references were by Winterberg[1] and Wenckebach and Winterberg;[2] the alternation was shown in a series of twenty and twelve cycles,

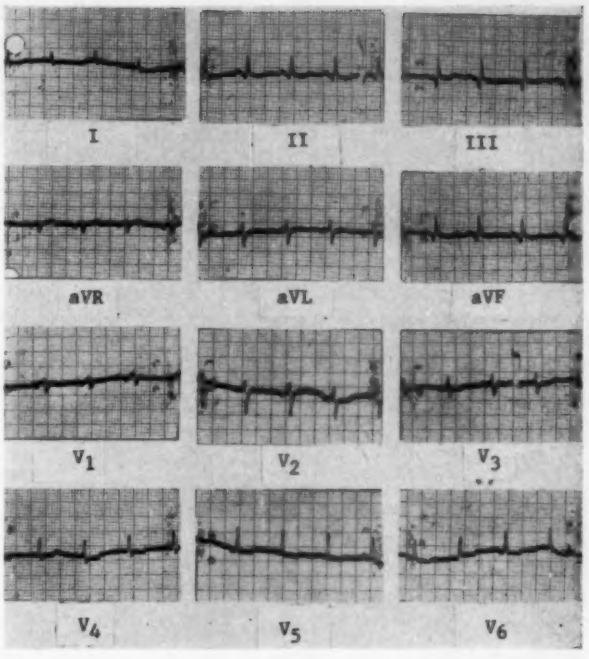

FIG. 4. Electrocardiogram taken same day as Figures 2 and 3. Cardiac rate is slower; all QRS complexes are of normal duration.

respectively. There was considerable variation in P-P, P-R and R-R intervals due to A-V heart block; also, aberration of the "normal" QRS of the alternation and ratios other than 2:1. These cases therefore were not included in our review.

Of the thirteen accepted cases (Table I), seven patients were women and six were men; ages ranged from forty-three to eighty-five years. Hypertension was common, being noted in nine cases; in six the systolic pressure was 200 mm. Hg or more. Hypertensive or arteriosclerotic heart disease was diagnosed in eleven cases. Hyperthyroidism and hyperparathyroidism were each present in one patient. Cardiac failure was observed in six patients. Digitalis was known to be taken at the time of the alternation in three patients, atropine in one and corphyllamine (euphyllin) in one; vagus pressure and/or exercise was utilized in four.

The type of bundle branch block was considered left-sided (presently accepted terminology) in ten cases. Most of the reports were made before 1944 and only three standard leads were recorded. A tall R wave in lead I and a deep S wave in lead III were present; in none of the ten was there a significant S wave in lead I. In two cases the block was right-sided

TABLE I
Thirteen Reported Cases of 2:1 Bundle Branch Block

Authors	Age (yr.) and Sex	Diagnosis	Cardiac Failure	Bundle Branch Block	P-R (sec.)	Rate (per min.)
Leinbach and White[4]	65,M	HCVD	0	Left	0.12–0.13(N) 0.14–0.16(B)	105
Stenstrom[3]	43,F	HCVD	0	Left	0.16(N) 0.17–0.18(B)	97
Kelly[5]	61, F	HCVD	+	Left	0.12–0.16	140
Donath[14]	50, F	HCVD	+	Left	0.14	136
Master et al.[15]	47, F	HCVD AMI	0	Left	0.16–0.18	103–111(N) 97–103(B)
Boyer[7]	64,M	Hyper-thyroidism	?	Left	Normal	136–140
Rasario[16]	66,M	HCVD	+	Left	Normal	95–100
Geill[17]	85,M	HCVD	+	Unknown	0.12(N) 0.14(B)	100
Kisch and Grishman[18]	47,M.	AMI	0	Left	0.16	100
Sandberg et al.[8]	57,M	ASHD Hyperpara-thyroidism	0	Left	0.16	107
Sandberg et al.[8]	52,M	HCVD	0	Right	0.14–0.16	139
Shearn and Rytand[10]	60,M	CVA HCVD	+	Left	0.14–0.17	103–107
Vesell and Levine	62,M	ASHD AMI	+	Right	0.13	137–142

HCVD = hypertensive cardiovascular disease; ASHD = arteriosclerotic heart disease; N = QRS is normal; B = QRS is wide.

and in one the QRS waves were concordant in the three limb leads.

The recorded duration of the 2:1 bundle branch block was from six to 138 cycles, most often between fourteen and twenty-five. In one case the alternation was said to have continued for five minutes and in another for eight minutes. The cardiac rates during the period of 2:1 bundle branch block were from 95 to 140 per minute. This was always a change from the rate during the period preceding or following the alternation when electrocardiograms were noted for these periods.

Electrocardiograms for the period preceding the alternation were reported in nine cases. In five of these complete 1:1 bundle branch block was present, one with a faster cardiac rate, three with a slower rate and in one the rate was not stated. In the other four of these nine cases unstable bundle branch block was present with a critical heart rate for transitions between normal and prolonged intraventricular conduction; slower in two, faster in one and unknown in one.

Electrocardiograms for the period following the alternation were recorded in twelve of the thirteen cases. Complete 1:1 bundle branch block was present in two, both with slower cardiac rates. In seven the intraventricular condition time was normal, all with a cardiac rate slower than during the 2:1 bundle branch block, in three there was unstable bundle branch block, all with a critical heart rate slower than the rate during the alternation.

During the period of 2:1 bundle branch block the alternate ventricular complexes with the normal QRS intervals frequently had an abnormal configuration. In these marked left

TABLE I (*cont.*)

Duration (cycles)	Preceding Conduction and Rate	Succeeding Conduction and Rate	Remarks
30 and 27	Unknown	BBB 1:1 95	T_1, T_2 inverted with normal QRS
Less than 1 minute	Unstable bundle branch block critical rate 82–85	Unstable bundle branch block slower	2:1 bundle branch block after digitalis, vagus pressure and exercise
22	Unknown	Bundle branch block 1:1 105	Bundle branch block 1:1 after digitalis
"5 min." 6 cycles recorded	Bundle branch block 1:1	Normal, slower	2:1 bundle branch block after corphyllamine I-V
16	Bundle branch block 1:1 95	Normal 85	Bundle branch block for 4 weeks
"8 min."	Bundle branch block 1:1 100–103	Normal, slower	2:1 bundle branch block after atropine I-V
14	Unstable bundle branch block 97–100	Normal 90	Bundle branch block other than 2:1 with vagal pressure
26	Normal in 1926	Normal 80	Intermittent bundle branch block with exercise or atropine
21	Bundle branch block 1:1	Not given	"True cardiac alternation"
20 and 27	Unstable bundle branch block; critical rate 78	Unstable bundle branch block; critical rate 85	Blood calcium 12–16 mg.
14	Bundle branch block 1:1 109	Normal 71	2:1 bundle branch block followed 2 step test
9	Unstable bundle branch block	Unstable bundle branch block; critical rate 83–94	3:1 and 4:1 bundle branch block also present
138	Bundle branch block 1:1 142–148	Normal 100–115	Critical rate for 2:1 bundle branch block

AMI = acute myocardial infarction; CVA = cerebrovascular accident, probably hemorrhage.

axis deviation of mean QRS was common. Q waves significant of myocardial infarction of the posterior wall were present in the electrocardiogram with an aVF lead; T waves in leads I or II were frequently inverted, in some as secondary changes, part of a left ventricular hypertrophy and strain pattern, in others as primary RS-T changes due to digitalis or myocardial ischemia. Alternation of heart sounds with the 2:1 bundle branch block was noted by Leinbach and White,[4] and by Kelly[5] who found no alternation in blood pressure.

CLASSIFICATION OF PARTIAL BUNDLE BRANCH BLOCK

Bundle branch block in general has been classified like A-V block into incomplete, partial and complete.[2,3,6] Partial bundle branch block has been divided into type I (Wenckebach) in which the QRS complexes gradually increase in width to that indicating complete blockage through one main bundle branch, and type II (Hay) with dropped "beats," 2:1: 3:1, 4:1, etc. bundle branch block, without transitional QRS complexes. 2:1 bundle branch block may be a form of partial bundle branch block, either type I (rarely if ever seen and proved) or type II.[19,20]

Group 1 (Alternation in Cardiac Rate): The cases of 2:1 bundle branch block reviewed in this report can be divided into three groups on the basis of specified changes in cardiac rate. Accordingly, group 1 consists of those cases in which, during the alternation, the cycle preceding each QRS complex of normal width is longer than the cycle preceding the adjacent wide QRS. The conditions for the changes in conduction here are the same as in ordinary

intermittent bundle branch block, i.e., induced by fatigue, vagus or sympathetic effects, rate, chemical and nervous changes. The role of a critical heart rate has been described[9,21] and recently emphasized.[10] An unstable state between conduction and block is believed present in the His-Tawara system, usually due to disease. In this setting an increase or decrease in cardiac rate can trigger the bundle branch block. An effective rate change has been found to be as little as one beat per minute or less than 0.01 second per individual beat at a cardiac rate of 100. The transition from conduction to block or vice versa most often occurs within the interval of just one cycle, and it can take place many times within a minute. Auxomerous condition has been suggested.[21] Friedman pointed out that heart rate is never absolutely constant even at rest and that in pulsus alternans careful measurement of the cycle length often showed prematurity of the weaker beats.[22] This occurred in six or eight of his own cases and in many reported by others. He indicated that at a rapid heart rate slight alternation in cycle length may contribute to the development of mechanical alternation. Such alternation in cardiac rate may be responsible for alternation of conduction in group 1. By calculation this variation in rate should be at least 0.03 second or more when the QRS of bundle branch block is 0.12 second and the normal QRS 0.08 second.[6,23] However, observations in ordinary intermittent as well as 2:1 bundle branch block indicate it can be less than 0.03 second.[7,9,19,23] Some or all of this variation in alternate cycle length is in duration of systole or QRS interval.

If in 2:1 bundle branch block only half the number of impulses traverse the fatigued bundle branch or its defective portion, this part should have a recovery period twice as long as for the contralateral bundle.[24] This should be the basis for a stable and persistent 2:1 bundle branch block. The alternation should be perpetuated even with a constant cardiac rate or with paradoxical rate change.[24] It should be frequent as is 2:1 A-V block. But 2:1 bundle branch block is infrequent. Its great rarity, according to Wilson, is due to the fact that in bundle branch block the impulse is not prevented from reaching the farther side of the region of impaired conductivity. Arriving from the contralateral side within 0.04 second, he believed it would allow no improvement in the conductivity of the region of block as a result of failure of the impulse to traverse it.[6] However, the exact pathway and type of conduction beyond the site of block in a main bundle branch still does not appear to be definitely established. Recent pertinent and elaborate investigations by Scher[25,26] and Sodi-Pallares[27,28] and their colleagues, and reasonings by Grant[29] are in substantial disagreement concerning this pathway in specific conduction and in common myocardial tissue in bundle branch block. Elucidation of the definite mechanism of 2:1 bundle branch block awaits a better solution of the problem of intraventricular conduction in common bundle branch block.

Group 1 is not true alternans. The 2:1 arrangement is fortuitous based on small but adequate variations in rate of individual beats and critical rate phenomena. In the case of Boyer[7] fourteen cycles of 2:1 bundle branch block are shown (his Fig. 3) in which by our measurements cycle lengths preceding the normal QRS were 0.44 to 0.45 second, and before the wide QRS 0.41 to 0.43 second. Each cycle before a normal QRS was 0.02 to 0.03 second longer than the preceding cycle before the wide QRS. This case and one reported by Slater of 3:1 and 4:1 bundle branch block[19] fit in the category of group 1.

Group 2 (Alternation Due to Supernormal Recovery Phase): Group 2 consists of cases of 2:1 bundle branch block in which the cycle preceding the normal QRS complex is regularly shorter than the one preceding the adjacent wide QRS. The cardiac rate is about 100 per minute. The alternate normal ventricular conduction (normal QRS) can be explained by the supernormal phase of recovery,[11,30,31] the slightly faster rate of alternate beats being just suitable for this. The supernormal recovery phase has been calculated at about 0.40 to 0.64 second after the onset of QRS.[32] Alternation due to supernormal recovery phase has been reported for A-V conduction in a small number of cases.[31,33] One of the aforementioned cases[15] of 2:1 bundle branch block had the characteristics of group 2. During the period of alternation the cardiac rate was about 100 (103 to 111) for the cycles immediately preceding the normal QRS, and 97 to 103 before the bundle branch block complexes. Cycles were 0.02 to 0.08 second shorter before the normal complexes, so that at intervals of 0.54 to 0.58 second the QRS complexes were more within the supernormal recovery phase. In the case

of Rasario[16] also, during the alternation the cycle preceding the wide QRS complex was longer than that before the QRS complex of normal width and the cardiac rate was about 100. Others of the above thirteen cases might have fallen into group 1 or 2 if some of the illustrations were better technically so that more precise measurements could be made.

Group 3 (True Cardiac Alternans): Group 3 is composed of cases of 2:1 bundle branch block in which the cycles are of constant length or in which they are inconsistently longer or shorter in relation to the two types of QRS complexes. In this group belong the instances of true cardiac alternans where there is no clear explanation for the mechanism of the 2:1 pattern such as in groups 1 and 2, and the regular alternation in two consecutive beats is not due to alternation of the time sequence. Alternation in bioenergetics of the heart and "alternans predisposition" have been described for inotropic processes.[34,35] Such chemical, electrical or mechanical changes may affect not only muscle contraction but also velocity of conduction and excitability[36] to produce a state of partial refractoriness of the conduction fibers, favorable for 2:1 intraventricular block. Kahn[37] had been able to produce a combination of pulsus alternans with alternation of bundle branch block by injection of glyoxalic acid in dogs. Katz[38] thought 2:1 intermittent intraventricular block a variant of ordinary electrical alternans. More recently, Kleinfeld et al.[39] have reported alternation of the membrane action potential of ventricular fibers of the frog heart following the administration of thyroxine or tri-iodothyronine, or after acute anoxia. They observed alternation of different phases of the membrane action potential, occasionally simultaneous with alternation in the isometric tension record. Bing and his colleagues[40] also recorded alternation in height of action potential associated with alternation (concordant) of contractions. They employed single cardiac muscle fibers of guinea pig ventricle to which aconitine had been applied and tachycardia produced. Of special note was that each fiber punctured during the alternation showed action potentials with every beat, making it unlikely that some myocardial cells take part in every second beat only and are refractory during the alternate cycle as frequently assumed.

Group 3A: In group 3 there are two subgroups. In group 3A the whole period of 2:1 bundle branch block occurs at a faster cardiac rate than the period of normal intraventricular conduction and at a slower rate than the complete 1:1 bundle branch block. The refractoriness or responsiveness of the affected bundle branch is further influenced by changes in cardiac rate for the whole period of 2:1 block rather than by variations in rate just for the individual beats as in groups 1 and 2. It is thus more closely allied to 2:1 A-V block. Though it is frequently difficult to eliminate variations in rate as a contributory cause of the partial block in the cases of group 3A, the chief mechanism of the 2:1 bundle branch block in some cases in this group may be that of true cardiac alternation unrelated to changes in heart rate.[18] Electrocardiograms taken prior to the alternation were available in nine and postalternation tracings were available in twelve of the thirteen cases. Complete 1:1 bundle branch block with a faster cardiac rate was present in one of these. Persistently normal intraventricular conduction time with a slower cardiac rate or unstable bundle branch block with a slower critical rate was present in seven others; thus eight cases could be placed in group 3A. Two of the eight cases (Master et al.[15] and Rasario[16]) belong in group 2.

Group 3B consists of those cases in which the period of partial 2:1 bundle branch block occurred at a faster heart rate than the period of complete 1:1 bundle branch block as in the case of Boyer.[7] His explanation of the 2:1 block, concurred in by Ashman,[36] was as follows: During the complete 1:1 bundle branch block each impulse passed far enough into the damaged branch at each cycle to retain some degree of refractoriness. With the rise in cardiac rate from 100 to 140 per minute, high and complete refractoriness resulted with complete blockage of the impulse. Therefore, recovery of the area was not interrupted so the next beat could pass. This was followed by complete refractoriness for the third beat and thus the 2:1 rhythm of bundle branch conduction continued while the rate remained high. Because of aforementioned reasons, in particular those of Wilson[6] and of Bing,[40] and especially the extreme rarity of 2:1 bundle branch block, such explanation is difficult to accept. The mechanism of 2:1 bundle branch block in group 3B remains obscure.

In the available pre- and postalternation tracings complete 1:1 bundle branch block with a cardiac rate slower than during the alternation

was present in four cases. One of these four (Boyer[7]) had been placed in group 1. Consistently normal intraventricular conduction time at a faster rate and unstable intraventricular conduction with a faster critical rate were not observed. There were thus three cases in group 3B.

Comment: The above findings suggest some correlation between 2:1 bundle branch block and cardiac rate. At least three cases demonstrated the presence of alternation of block with alternation of rate for individual beats. Many showed a correlation between 2:1 bundle branch block and changes in cardiac rate for the whole period of alternation compared to the rate when the intraventricular conduction was normal for each beat. The small number of cases available do not allow more general conclusions on the relationship between chronotropism (variations in rate) and dromotropism (variations in conduction) in 2:1 bundle branch block.

Summary

A case of 2:1 bundle branch block is described. All 138 consecutive ventricular complexes recorded in the routine twelve lead electrocardiogram were of this pattern. Only twelve other acceptable cases of 2:1 bundle branch block were found in a review of the literature. A synopsis of these is given. The mechanism of production of 2:1 bundle branch block is discussed, especially in regard to critical rate phenomena, theories of the site of delay in bundle branch block and especially in regard to the great rarity of 2:1 bundle branch block. The cases of 2:1 bundle branch block are classified into three groups on the basis of specified changes in cardiac rate.

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Lymph Node Compression of the Pulmonary Artery Causing a Continuous Murmur*

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SINCE THE CLASSIC description of the continuous murmur in patent ductus arteriosus by Gibson[1] in 1900, numerous causes of continuous murmurs have been described (Table I).

TABLE I

Some Conditions in Which Continuous Murmurs Have Been Described

I. Communications between high and low pressure systems
  A. Extracardiac
    1. Aortic-pulmonary artery communications
      a. Patent ductus arteriosus[1]
      b. Aorticopulmonary fenestrations[2]
      c. Surgical anastomoses[3,4]
      d. Rupture of congenital or acquired aneurysms of the sinus of Valsalva into the pulmonary artery[5]
    2. Arteriovenous fistulas
      a. Congenital
        1. Pulmonary[6]
        2. Wall of the chest[7]
        3. Subclavian artery and vein[8]
      b. Acquired[7]
        1. Traumatic
        2. Mycotic
  B. Partially intracardiac
    1. Rupture of congenital or acquired aneurysms of sinus of Valsalva into various cardiac chambers[9]
    2. Communications between the coronary arteries and the cardiac chambers[10] or the coronary sinus[11]
    3. True truncus arteriosus
    4. Complicated congenital defects with multiple anomalies[12]
II. Dilated channels
  A. Venous hum
    1. Children[13]
    2. Thyrotoxicosis[14]
    3. Cirrhosis[15]
    4. Mammary souffle[16]
  B. Collateral arterial channels
    1. Coarctation of the aorta[17]
    2. Pseudotruncus (pulmonary atresia)[18]
III. Partial constriction of a vessel
  A. Aortic arch syndrome[19]
  B. Segmental stenosis of pulmonary artery[20]

It is the purpose of this paper to report a case in which such a "Gibson" murmur arose from extrinsic compression of the left pulmonary artery by an enlarged lymph node, a heretofore unreported cause of continuous murmur. The location and character of the murmur suggested the diagnosis of patent ductus arteriosus.

CASE REPORT

An eighteen year old white woman was admitted to University Hospital on August 14, 1959, because of dyspnea. She had been in excellent health until one year before admission when she noted the onset of attacks of dyspnea characterized by slow, deep respirations associated with a sensation of severe shortness of breath. These episodes lasted approximately five minutes and initially occurred once every two to three months. They had increased in frequency, however, and by the time of admission were occurring as often as three to four times in twenty-four hours. At first, her family physician considered these attacks hysterical in nature, but several weeks before admission a heart murmur was heard.

There were no other cardiorespiratory symptoms. Birth, growth, development and activity were normal. There was no previous knowledge of a cardiac murmur. The patient had lived on a farm in Ohio all her life. Her past history was otherwise non-contributory. A twenty-four year old sister was under the care of a physician for attacks of dyspnea identical to those suffered by the patient. Otherwise the family history revealed nothing abnormal.

Physical examination revealed a well developed, well nourished young woman in no acute distress. The positive findings were limited to the cardiac examination. The apex impulse was well localized in the fifth left intercostal space within the midclavicular line. No thrills were palpable and there was no evidence of cardiomegaly. The first heart sound was split at the apex. The second pulmonic sound was split and was louder than the second aortic sound. There was a grade 4, medium pitched, continuous, blowing murmur well localized in the second intercostal space

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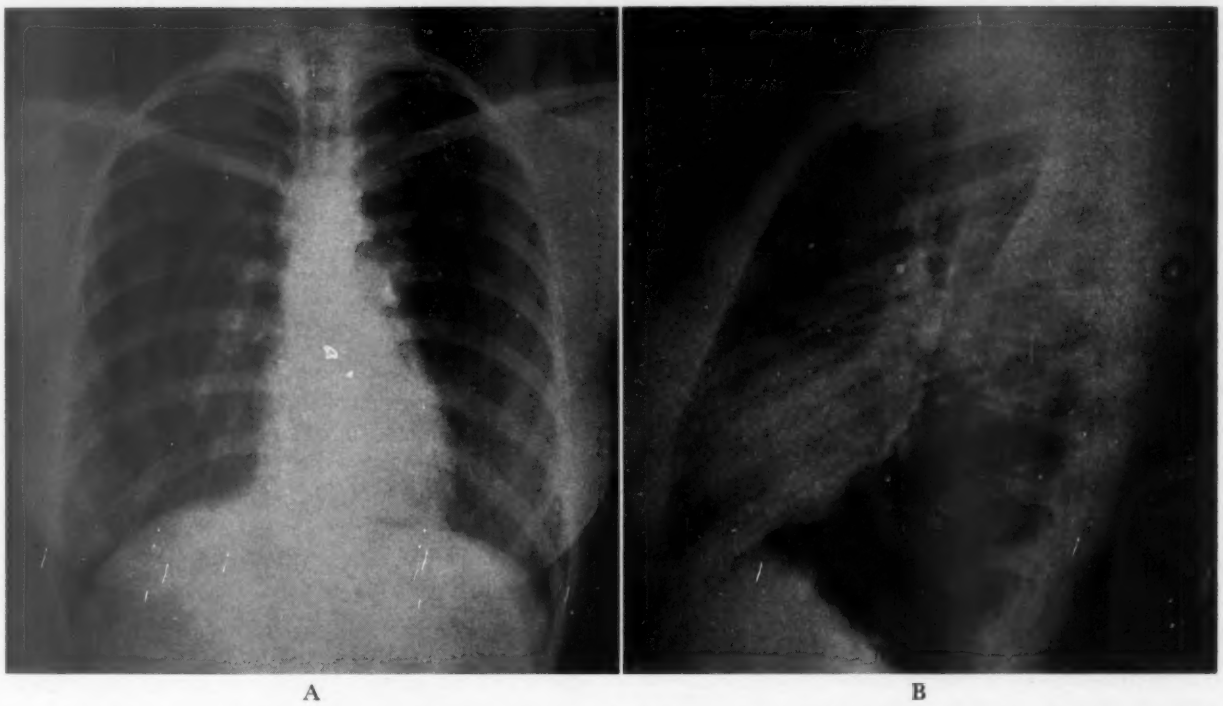

A B

FIG. 1. A, posteroanterior teleoroentgenogram showing multiple small calcified nodules throughout both lung fields in addition to three nodules, each 1 cm. in diameter, one of which overlies the left pulmonary artery. B, left lateral teleoroentgenogram showing one of the larger nodules lying anteriorly behind the sternum and the other two located in the hilar region.

immediately to the left of the sternum, with minimal radiation toward the left infraclavicular area. The murmur was louder in systole with late accentuation and did not vary with position of the head or pressure on the stethescope. All pulses were easily palpable, the radial and femoral pulses occurring simultaneously. Her temperature was 98.6°F., pulse 68 beats per minute and regular and respiration 16 per minute. The blood pressure was 104/60 mm. Hg in the arms and 125/70 mm. Hg in the legs.

Laboratory Findings: Complete blood count, urinalysis, blood urea nitrogen, blood sugar, total protein, albumin/globulin ratio, antistreptolysin O titer and sedimentation rate were normal. Serologic tests for syphilis and C-reactive protein were negative. Purified protein derivative No. 2 skin test was negative after twenty-four and forty-eight hours. The histoplasmin skin test (1:100) was strongly positive. The histoplasmin complement fixation and collodion agglutination tests were negative. The electrocardiogram was within normal limits.

Radiographic Findings: A roentgenogram of the chest (Fig. 1A) showed numerous calcified nodules 3 mm. in diameter scattered throughout both lung fields. In addition, there were three nodules, each 1 cm. in diameter, located in the parahilar regions, one on the right and two on the left. One of these nodules was seen to overlie the left pulmonary artery. A lateral view of the chest (Fig. 1B) showed one of the nodules lying immediately behind the sternum while the other two were in the hilar region. With cardiac fluoroscopy the heart was found to be normal in size with no specific chamber enlargement. The pulmonary vascularity and pulsations were normal. The aorta was normal in size as was the pulmonary artery although the overlying calcified nodule gave a false impression of enlargement of the left pulmonary artery at the first examination.

Differential Diagnosis: Diagnosis on admission to the hospital was patent ductus arteriosus although there was some doubt concerning the accuracy of this diagnosis. The symptoms appeared to be typically psychogenic and in all probability not of cardiac origin. The normal electrocardiogram, cardiac fluoroscopy and pulmonary vascularity cast further doubt on the diagnosis. The murmur, however, although somewhat higher pitched than the usual ductus arteriosus murmur, was continuous and characteristic in location. Most of the known causes of continuous murmurs were excluded by the physical examination, roentgenogram, electrocardiogram and the apparent hemodynamic insignificance of the lesion. A small communication between the aorta and pulmonary artery seemed the most probable diagnosis. It was believed that a lesion too small to produce demonstrable hemodynamic changes might be impossible to demonstrate by cardiac catheterization or aortography. Such a communication could, however, be the site of bacterial endarteritis and surgical exploration was therefore considered advisable.

Surgical Findings: On August 21, 1959, the left side of the chest was entered through a posterolateral incision. Dense adhesions were found between the anterior segment of the upper lobe of the left lung and the parietal pleura. A firm calcified nodule in the anterior segment was removed. A calcified lymph node measuring 1 cm. in diameter was found to overlie and compress the left pulmonary artery at which point a continuous thrill was felt. On removal of the lymph node, the thrill disappeared. The ligamentum arteriosum, 7 mm. in diameter, was then exposed. No thrill could be felt over it. On section there was a small amount of oozing from the severed ends but no evidence of patency. At this point in the procedure the surgeon was able to reproduce the continuous thrill by manual compression of the left pulmonary artery at the site of the lymph node removed previously. The postoperative course was uncomplicated and the patient was discharged on the seventh day following surgery. At no time during the postoperative period could a murmur be heard over the chest.

Pathologic examination of both the lung nodule and lymph node revealed a cystic structure with a fibrous wall containing necrotic cellular material. There was no evidence of active inflammation and the pathologist believed that the lesion was typical of a "burned-out" granulomatous process. In view of the negative purified protein derivative No. 2 skin test and the strongly positive histoplasmin skin test, inactive histoplasmosis was considered to be the most probable cause of the granuloma.

Discussion

In 1956, Myers et al.[21] presented an experimental explanation for the continuous murmur heard in the aortic arch syndrome. Partial ligation of blood vessels in dogs caused only systolic murmurs when the collateral vessels were intact; but when they, too, were obstructed, continuous murmurs were produced. Open collateral vessels insured blood flow into the vessel distal to the obstruction sufficient to maintain a diastolic pressure equal to that in the proximal segment. Collateral ligation lowered the pressure beyond the obstruction resulting in a constant pressure gradient and hence continuous blood flow. In the same paper, the authors discussed a case of occlusive disease of the lower aorta in which a systolic murmur over the vessel was converted to a continuous murmur after exercise. It was postulated that the vessels distal to the obstruction were emptied during exercise and could not be refilled during diastole since the collateral circulation was also obstructed. The diastolic pressure distal to the occlusion, therefore, fell and the constant pressure gradient resulted in a continuous murmur.

Eldridge et al.[20] in 1957 reported the cases of two patients in whom continuous murmurs arose from stenotic lesions of the main branches of the pulmonary artery. They were able to prove by cardiac catheterization that a pressure gradient across the constriction existed throughout systole and diastole. In a third subject with only a systolic murmur a pressure gradient was noted only during systole. These investigators were also able to produce continuous murmurs in animals by partial ligation of the aorta or pulmonary arteries, and demonstrated that such continuous murmurs are produced only when the degree of constriction is marked.

There seems to be little doubt that this continuous murmur was caused by external compression of the left pulmonary artery by an enlarged lymph node. The continuous thrill over the artery which disappeared with removal of the lymph node, the reproduction of the thrill by manual compression of the vessel, the absence of a patent ductus arteriosus and the disappearance of the murmur following surgery all support this conclusion. Lymph node compression of the pulmonary artery must now be added to the numerous causes of continuous murmurs over the chest.

This condition alone is, in all probability, of no clinical significance. Its importance lies in the fact that, as in the present case, it may be indistinguishable from instances of patent ductus arteriosus which are too small to produce the typical hemodynamic effects of left ventricular overloading. In patients with continuous murmurs and radiologic evidence of lymph nodes adjacent to the pulmonary vessels, the diagnosis of vascular compression could theoretically be made by angiocardiography.

Summary

A patient with lymph node compression of the left pulmonary artery is presented in whom a continuous murmur suggested the diagnosis of patent ductus arteriosus. The numerous causes of continuous murmurs are tabulated and the mechanism of the production of continuous murmurs by vascular narrowing is reviewed.

Acknowledgment

We are indebted to Dr. Karl Klassen, chief of the Department of Thoracic Surgery, who performed the exploratory thoracotomy and to Dr. Jacob Old of the Department of Pathology who reviewed the pathologic sections.

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Correction of Congenital Ventricular Septal Defect in a Patient with Previous Surgically Produced Pulmonary Artery Stenosis*

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IN 1952, Muller and Dammann[1] reported the treatment of large ventricular septal defects in children by the creation of pulmonary artery stenosis. This procedure decreased the excessive pulmonary blood flow which was due to the large left-to-right shunt and thereby increased the left ventricular output by diverting more blood systemically instead of through the lesser circulation.

The following is a report of an eight and a half year old girl with a large ventricular septal defect who, at the age of twenty months, was in severe heart failure which was alleviated by the creation of pulmonary artery stenosis. Recently, when her cardiac status again deteriorated, she was operated upon and cured by definitive open heart surgery. One other such case has been reported by Sirak, Hosier and Clatworthy.[2]

CASE REPORT

M. F. is an eight and a half year old white girl. At birth a systolic murmur was heard at the lower sternal border, but there was no evidence of heart failure. Although mental development was normal, her growth and physical development were retarded, so that at the age of twelve months she weighed only $17^1/_2$ pounds and her height was $29^3/_8$ inches. At fifteen months of age, cardiac failure was present as manifested by dyspnea, intolerance to exercise, slight cyanosis and a distended liver without ankle edema. The patient was unable to stand because of dyspnea. The electrocardiogram revealed biventricular hypertrophy, predominantly right. Roentgenogram of the chest showed cardiomegaly with a large pulmonary artery segment and fluoroscopy demonstrated engorged, pulsating pulmonary arteries.

Angiocardiography demonstrated a large ventricular septal defect. Because of the child's critical condition, Dr. J. Frank Dammann recommended creation of a pulmonary artery stenosis. On October 13, 1952, Dr. William H. Muller, Jr. created a pulmonary stenosis by removing a small wedge of pulmonary artery and suturing this area together to narrow the main pulmonary artery. In addition, a cellophane band was sutured around the stenosis. Pressures recorded prior to the creation of the pulmonary artery stenosis were 63/35 mm. Hg in the main pulmonary artery and 87/55 mm. Hg in the aorta. At the completion of this procedure the main pulmonary artery pressure was 102/78 mm. Hg; the distal pulmonary pressure, 49/27 mm. Hg; and the right ventrical pressure, 102/70 mm. Hg. The patient tolerated surgery well and began to improve immediately thereafter.

During the subsequent five years she was able to tolerate moderate activity and attended school where she achieved better than average grades. Her growth and physical development, while subnormal, were markedly accelerated as compared to the preoperative period. During her eighth year she had increasing fatigue, cyanosis upon moderate activity, loss of appetite and marked intolerance to exercise. There was no edema, cough or syncope. Because of this course, re-evaluation of her status was recommended, and she was admitted to St. Vincent's Hospital on February 24, 1959.

Physical Examination: The patient was a thin, somewhat pale, alert and intelligent girl weighing $47^1/_2$ pounds and measuring 50 inches in height. The blood pressure in both arms was 90/65 mm. Hg. There was no clubbing and no cyanosis at rest, but following exercise dyspnea and slight cyanosis developed. The venous pressure was not elevated, and neither hepatomegaly nor edema was present. The lungs were normal and all pulses were present and

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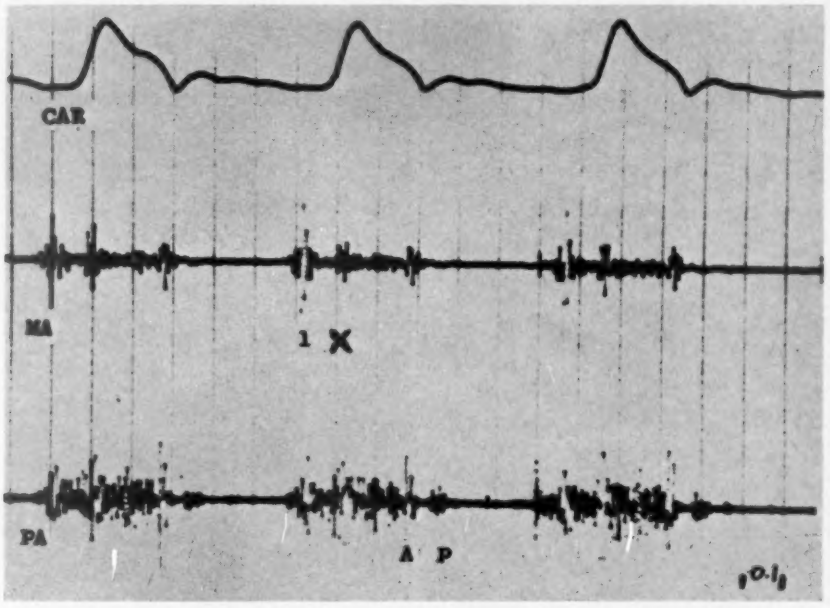


FIG. 1. The phonocardiogram demonstrates the murmurs at the mitral area (MA) and pulmonary area (PA) in relation to the carotid pulse. Note the ejection click (X) and the widely split pulmonary second sound (A and P). The time interval between vertical markings is 0.1 second.

equal. Examination of the heart revealed the apex beat just beyond the mid-clavicular line. There was a moderate right ventricular lift at the left sternal border. A systolic thrill was noted parasternally at the third and fourth intercostal interspaces; a second, more discrete, thrill was present over the pulmonary area. Auscultation showed both heart sounds to be audible in all areas, and the heart rhythm was regular. At the pulmonary area there was a wide splitting of the second sound with a delayed pulmonary element of normal intensity. Along the left sternal border a pulmonary ejection click could be heard. A grade 4 pansystolic murmur was heard along the parasternal border transmitted to the apex, and an ejection type murmur of slightly less intensity was at the pulmonary area. A phonocardiogram is shown in Figure 1.

Chest X-ray and Electrocardiogram: Cardiac x-ray films showed a transverse diameter of 10.8 cm. and a transthoracic diameter of 20 cm. (Fig. 2). The apex of the heart was elevated with an over-all configuration of right-sided enlargement. There was slight prominence of the main pulmonary artery with normal appearing hilar vessels and slightly diminished vascularity in the peripheral lung fields. The aorta appeared slightly smaller than normal. The electrocardiogram showed marked right ventricular hypertrophy (Fig. 3A).

Cardiac Catheterization and Angiocardiography: On February 29, 1959, right heart catheterization was performed. The data obtained at catheterization are shown in Table I. At the same time, selective angiocardiography was performed with the catheter tip in the subvalvular region of the right ventricle (Fig. 4). The data obtained from these studies led to the conclusion that this patient had a large ventricular septal defect with slight bidirectional shunting and a small effective right-to-left shunt. The artificially created pulmonary artery stenosis produced a significant gradient from the right ventricle to the pulmonary artery. The angiocardiogram accurately shows the stenotic area,

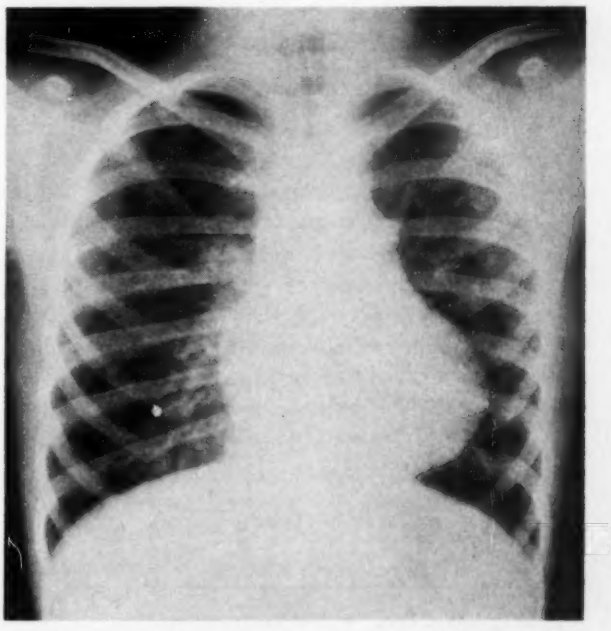


FIG. 2. Posteroanterior roentgenogram of the chest reveals cardiomegaly, predominantly right-sided.

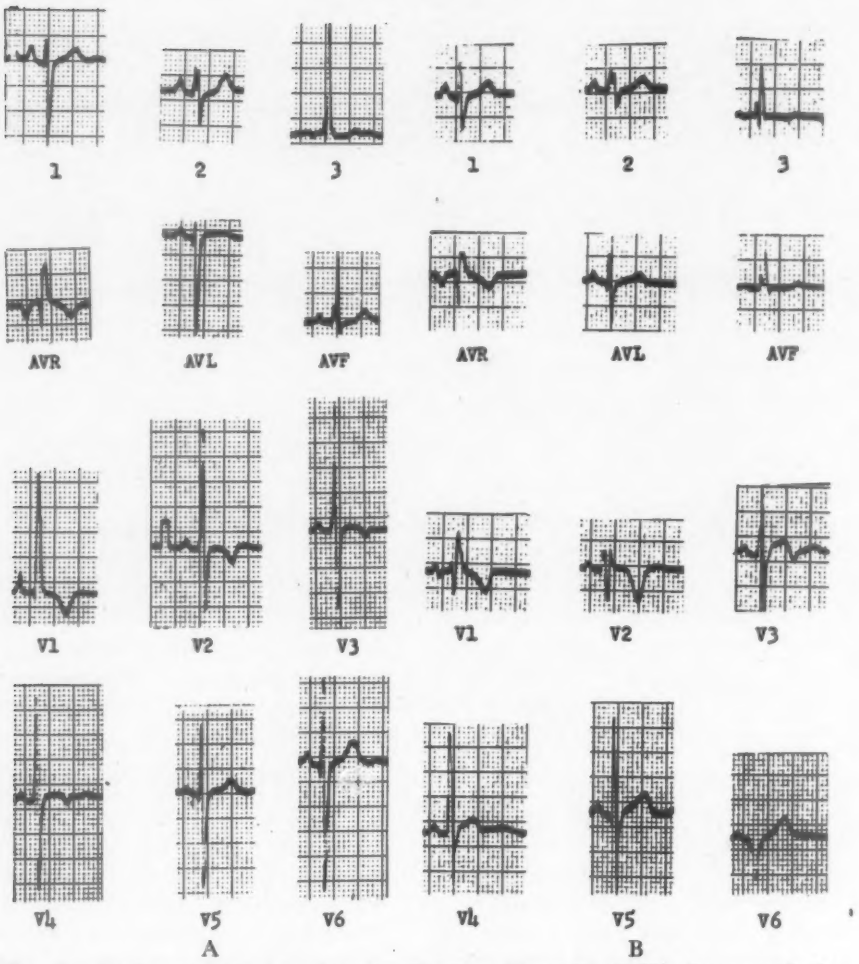


FIG. 3. A, the preoperative electrocardiogram (June 10, 1959) shows marked hypertrophy of the right ventricle. B, in the postoperative tracing (October 10, 1959) this has diminished substantially.

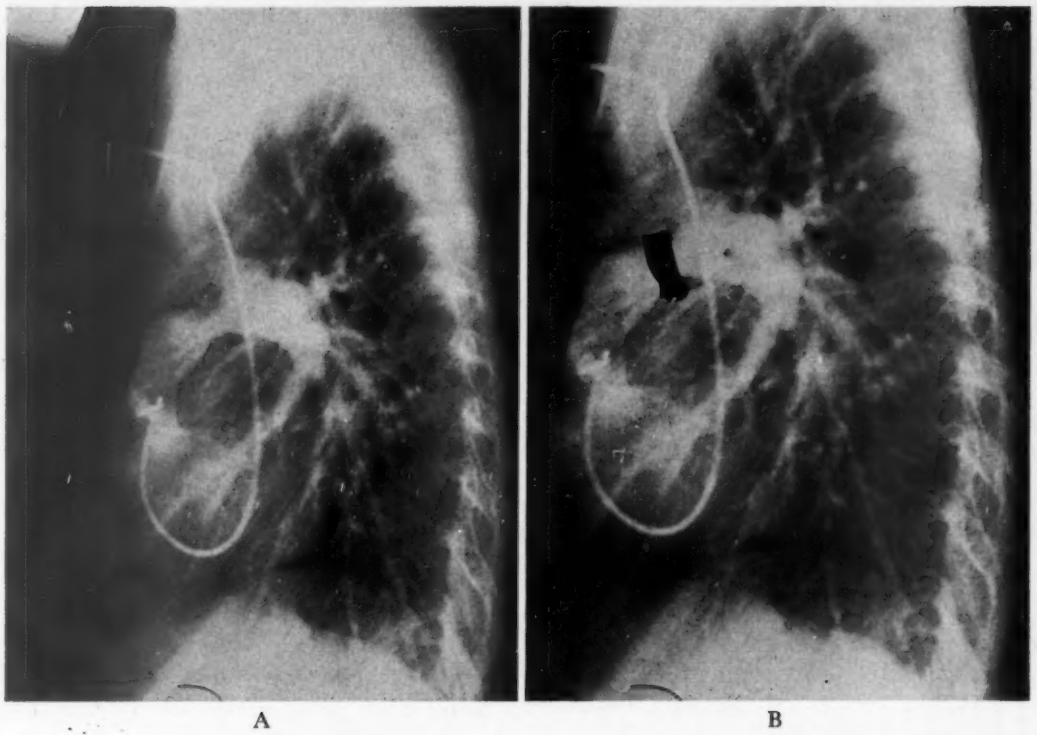
about 1.5 cm. in length, and reveals slight dilatation of the first inch of pulmonary artery beyond the constriction.

Surgical Treatment: On June 12, 1959, open heart surgery was performed. Through a median sternotomy incision, the pericardial sac was opened and examination revealed a constriction of the pulmonary artery approximately $1^1/_4$ cm. long. This was 5 mm. distal to the pulmonary valve and the lumen of the pulmonary artery at this area was narrowed to 6 mm. in diameter. The diameter of the pulmonary artery was 16 mm. both proximal and distal to the constriction. The patient was placed on cardiopulmonary by-pass, the right ventricle was incised and the area of constriction of the pulmonary artery was opened in a longitudinal direction along the former suture line. The piece of cellophane used to band the pulmonary artery (Fig. 4B) was completely removed, and the incision in the pulmonary artery was then sewed in a transverse direction, thereby correcting the pulmonary stenosis. A defect, 12 mm. in diameter, was present in the membranous portion of the ventricular septum. This defect was located immediately beneath the aorta behind the tricuspid valve. A compressed Ivalon® sponge was sewed into the area of defect using interrupted and continuous 4-0 sutures. The incision in the right ventricle was closed and the patient was taken off cardio-

TABLE I
CARDIAC CATHETERIZATION FINDINGS

Site of Catheterization	Pressure (mm. Hg)	Oxygen Saturation (%)
Superior vena cava	7.5/2	60
Left superior vena cava	...	59
Right atrium	12/2	61
Right ventricle	100/9	61
Outflow tract of right ventricle	...	66
Right pulmonary artery	28/6	69
Arch of aorta	100/62	92
Left ventricle	100/9	93

Systemic blood flow = 3.06 L./min.
Pulmonary blood flow = 2.83 L./min.
Effective shunt = 0.23 L./min. right to left.



A B

FIG. 4. A, preoperative angiocardiogram demonstrates the pulmonary artery stenosis. B, superimposed cellophane band removed at surgery.

pulmonary by-pass. Simultaneous pressures were taken in the right ventricle, pulmonary artery and femoral artery just prior to closure of the chest. Although the tracings were not completely satisfactory due to technical difficulties, they show a significant reduction in the gradient between the right ventricle and the pulmonary artery (Fig. 5).

Postoperative Results: The immediate postoperative course was essentially uneventful. Tracheobronchial suctioning was necessary during the first three days, but the patient gradually regained her strength and walked on the fifth postoperative day. There was no evidence of cardiac failure. At present, five months postoperatively, she is completely asymptomatic and tolerates the usual activities of a child her age without difficulty. The patient states that she can never remember feeling so well and being able to do so much. She is now 53 inches tall and weighs $54^1/_2$ pounds. The low systolic murmur and thrill have disappeared and the murmur and thrill over the pulmonary area are much less intense. A recent electrocardiogram (Fig. 3B) reveals diminution of the pattern of right ventricular hypertrophy.

COMMENTS

Ventricular septal defects range from the tiny, dynamically insignificant lesions to the very large ventricular septal defects which, in effect, create a single ventricle. The latter defects allow direct transmission of left ventricular pressure to the pulmonary vasculature. It is this condition, namely the large, high pressure ventricular septal defect which produces disability at birth or shortly thereafter, that applies to the subject of this report.

In general there are two major sources of circulatory failure in persons with ventricular septal defects: the extremely high pulmonary blood flow and increased cardiac work and the increased pulmonary resistance leading to progressive right ventricular enlargement and failure. These two factors are often combined. There are at least two possible mechanisms to account for the high pulmonary resistance so often associated with large defects. First is a persistence of the fetal state of the pulmonary arteries, implying failure of the thick, muscular fetal vessels to involute to the thin arteries of the normal state.[3,4] Second is the more frequent situation in which normal involution from the fetal state occurs but is followed by increased pulmonary resistance as a reaction to the high pressure flow.[4,5,6] It is probable that at first the pulmonary arteries react with local constriction eventually followed by thickening and narrowing of the lumen. In this circumstance the high resistance state will develop at a rate which varies from case to case, but in general

FIG. 5. Simultaneous pressures taken at surgery prior to closure of the chest, showing reduction of the gradient between the right ventricle and pulmonary artery (lower tracing). The time interval between vertical markings is 0.1 second.

this rate is related to the size of the defect. The smaller defect with a large gradient between the left and right ventricles is less apt to precipitate pulmonary hypertension.

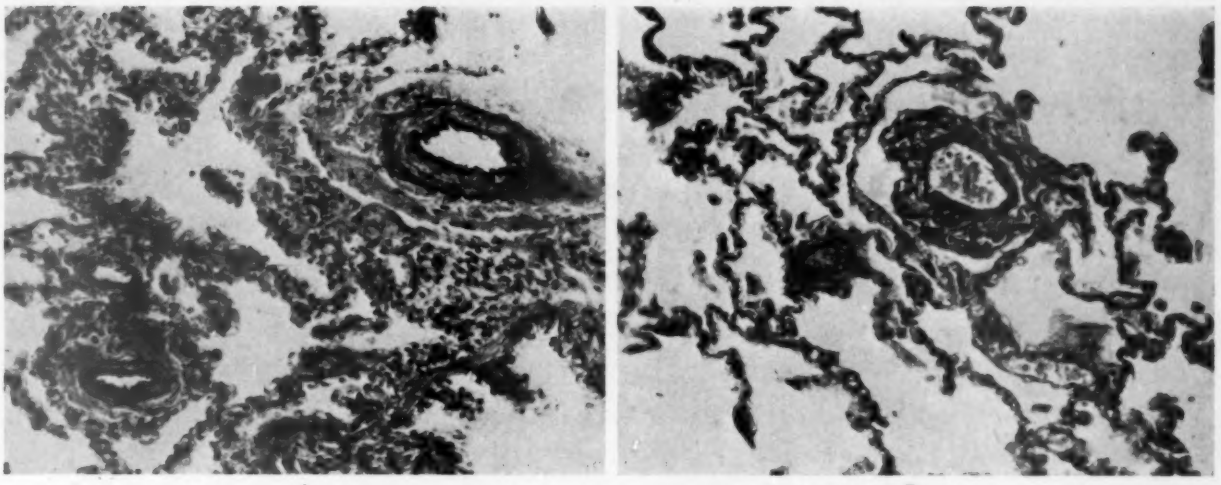
The creation of a pulmonary artery stenosis would probably be of value in infants with a common ventricular ejectile force and a large pulmonary blood flow leading to heart failure, for this procedure would divert left ventricular output away from the lesser circulation, thereby producing more effective systemic and coronary artery blood flow. In those cases associated with increased pulmonary vascular resistance due to reactive vasospasm or failure of involution of fetal type arteries, an artificial pulmonary artery stenosis would probably "rest" the peripheral pulmonary arteries and prevent the subsequent development of irreversible vascular sclerosis and thickening and might possibly produce involution of the previous changes. In those cases where marked late obliterative vascular changes have already occurred, the value of this procedure is questionable. Although the site of increased resistance would be shifted from the peripheral pulmonary arteries to the proximal artery, it remains to be determined whether right ventricular failure would ensue before possible reversal of peripheral obliterative changes has occurred.

In the case reported herein, the chief value derived from the creation of a pulmonary artery stenosis was the decrease in pulmonary blood flow with alleviation of the pulmonary congestion and an increase in systemic flow as expressed by the rapid and pronounced improvement following surgery. Pressures recorded at surgery demonstrated only moderate pulmonary hypertension at least in part the result of increased pulmonary blood flow, while the biopsy specimen of the lung obtained at the time of the initial surgery revealed only minimal pulmonary arteriosclerosis and differed slightly from the biopsy specimen taken during the patient's second completely-corrective open heart surgery (Fig. 6).

In summary, it would appear that the creation of a pulmonary artery stenosis might be indicated in the very small child weighing less than fifteen pounds, in whom there is a pronounced left-to-right shunt, when it is believed that the patient would not survive and reach fifteen pounds or more for open heart surgery. It is in this situation that the relatively simple procedure of creating a pulmonary artery stenosis might be used as a palliative operation to be followed at a later date by definitive surgery. The value of this procedure has not been determined in those cases where increased pulmonary vascular resistance is the primary cause of difficulty.

SUMMARY

A report is given of a patient with a large ventricular septal defect, in whom the creation of an artificial pulmonary artery stenosis at the



A B

FIG. 6. A, the biopsy specimen of the lung taken at the time the pulmonary artery stenosis was created shows minimal pulmonary arteriolar sclerosis. B, the biopsy specimen taken seven years later is essentially normal. x 150.

age of twenty months reversed severe heart failure and allowed her to live a reasonably normal life for the subsequent five years. At the age of eight years, cardiac failure once again presented a threat and the patient was completely cured by definitive open heart surgery.

The creation of a pulmonary artery stenosis may be considered in tiny infants with this condition who are under fifteen pounds and who are in circulatory failure because of increased pulmonary blood flow associated with diminished systemic blood flow.

ACKNOWLEDGMENT

The authors gratefully acknowledge the cooperation of Dr. J. Frank Dammann who supplied much of the data concerning the earlier phase of the patient's illness.

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Ruptured Intracranial Aneurysm Associated with Coarctation of the Aorta

Report of a Patient Treated by Hypothermia and Surgical Repair of the Coarctation*

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IN THE PAST, the association of a ruptured intracranial aneurysm with coarctation of the aorta has been almost invariably fatal. Increased awareness of this problem and the early use of arteriography may allow more patients to be correctly diagnosed antemortem. Antihypertensive drugs, hypothermia, safer anesthesia and better neurosurgical and thoracic surgical technics should greatly improve the previously grave prognosis of patients with this condition.

The following case is believed to be the first such case in which hypothermia was utilized and in which the coarctation was surgically repaired during the acute phase of intracranial bleeding.

CASE REPORT

V. G., a fourteen year old white male of Italian descent, was admitted to the hospital on June 5, 1958, because of a syncopal episode on the day prior to admission.

Past History: The patient had a normal birth and development. At six years of age a cardiac murmur was heard for the first time and two years later hypertension was discovered. The patient was referred to the Pediatric Clinic for further evaluation. His general appearance seemed normal. Blood pressure in the right arm was 168/110 mm. Hg and in the left arm 160/100 mm. Hg. No blood pressure could be obtained in the lower extremities. Examination of the heart revealed a loud harsh basal systolic murmur which was transmitted to the neck and to the left axilla. The pulmonic second sound was greater than the aortic second sound. Femoral pulses were diminished bilaterally; the popliteal and pedal pulses were not palpable. There was no cyanosis or clubbing. Fluoroscopic and roentgenographic examination of the chest revealed a normal cardiac contour, localized dilatation of the aortic knob and slight notching of the ribs. An electrocardiogram showed right axis deviation but no chamber hypertrophy. A diagnosis of coarctation of the aorta was made, and it was decided to observe the patient in the clinic and to schedule him for surgery at a later date.

The child remained entirely asymptomatic although his blood pressure ranged from 140/80 to 160/90 mm. Hg. Roentgenograms of the chest in 1955 revealed left ventricular hypertrophy and marked notching of the ribs (Fig. 1). The boy's parents were repeatedly urged to bring the child into the hospital for corrective surgery, but they were reluctant to do so because of his apparent excellent state of health.

Present History and Clinical Findings: On June 4, 1958, the patient exhibited bizarre behavior in school and fainted while walking home. He was found unconscious in the street. There was no evidence of head trauma, tongue biting or clonic movements of the extremities. He regained consciousness spontaneously, and was admitted to another hospital for observation. That evening he became lethargic, vomited several times and complained of dull frontal headache. The next morning he was transferred to The Mount Sinai Hospital.

On admission to the Pediatric Service he appeared irritable and drowsy but he was well oriented. The blood pressure in the right arm was 156/100 mm. Hg, in the left arm, 148/94 mm. Hg. All other vital signs were normal. The left border of cardiac dullness extended to the anterior axillary line. The murmurs were unchanged from previous examinations. A systolic thrill was palpated over the right carotid artery. The aortic second sound was louder than the pulmonic second sound. Visible prominent pulsations were noted in both axillas and in the intercostal grooves of the lateral chest wall. Neurologic exam-

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ination revealed the deep tendon reflexes to be hypoactive. Minimal nuchal rigidity was present; however, the straight leg raising test was negative. There was a right extensor plantar response. During the ensuing four hours the patient became more drowsy and meningeal signs increased in intensity.

Lumbar puncture revealed an initial pressure of 270 mm. H_2O and grossly bloody cerebral spinal fluid. Microscopically, both fresh and crenated red blood cells were seen. The supernate was xanthochromic. The protein content was 390 mg. and the sugar was 46 mg./100 ml. Cultures of the spinal fluid were negative. A complete blood count, fasting blood sugar, blood urea and electrolytes were normal. A trace of albumin and an occasional granular cast were present in the urine. Blood culture and tuberculin skin test were negative. Electrocardiogram and chest x-ray film were unchanged from previous examinations. *The clinical impression* was coarctation of the aorta complicated by hypertension and acute subarachnoid hemorrhage.

Clinical Course: The patient's neurologic status remained unchanged for four days; then his condition became worse (Fig. 2). He complained of headache, appeared more drowsy and the meningeal signs increased. Concomitantly, blood pressure and temperature rose steadily. An electroencephalogram showed diffuse slowing, most marked in the right posterior cerebral region, less strongly accentuated in the left temporal region. On the fifth day his temperature reached 104°F., and blood pressure rose to 190/120 mm. Hg. Reserpine, (4 mg.) was given intramuscularly, and the blood

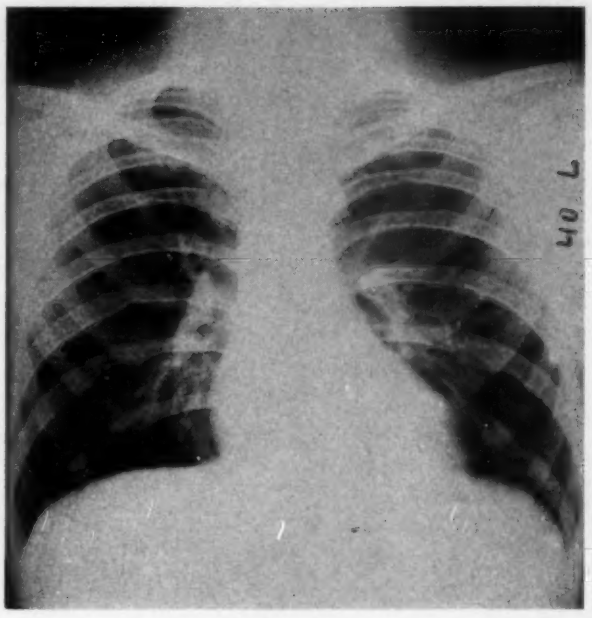


FIG. 1. Posteroanterior chest film illustrating bilateral notching of the ribs and left ventricular hypertrophy.

pressure fell to 146/70 mm. Hg. Blood pressure was maintained at this level for the next four days by oral reserpine, 0.25 mg. four times a day. On the sixth hospital day he experienced a brief episode of mental confusion. A bilateral Babinski response was noted at this time. Lumbar puncture revealed an initial pressure of 270 mm. H_2O. The cerebral spinal fluid was pink; the supernate was xantho-

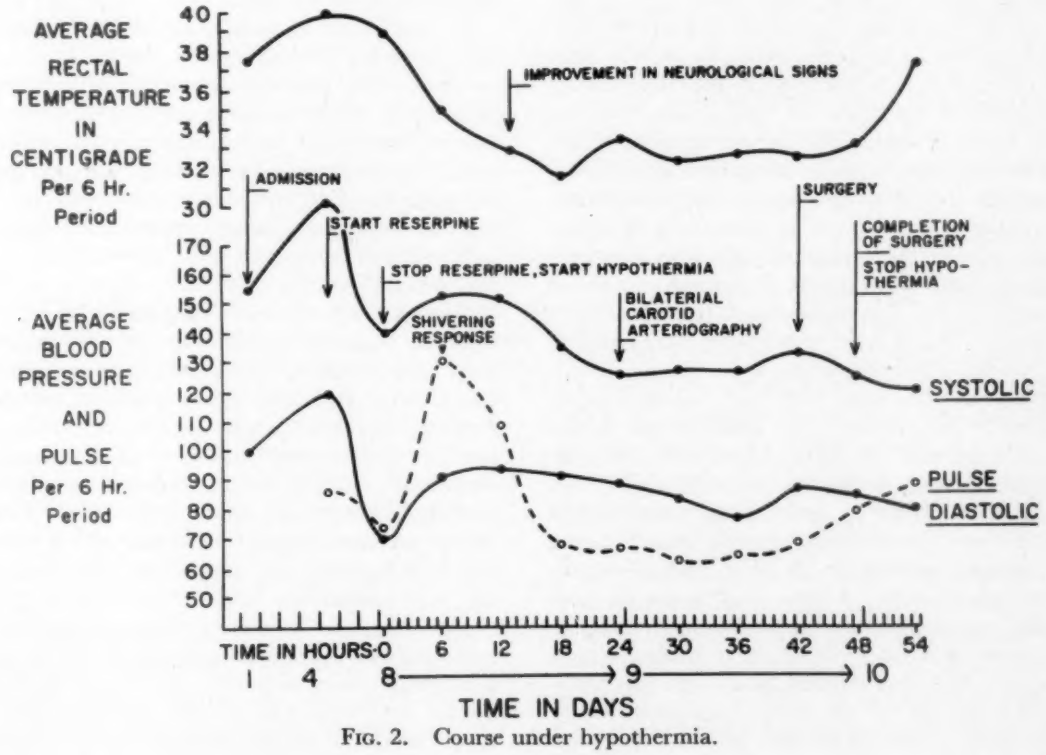
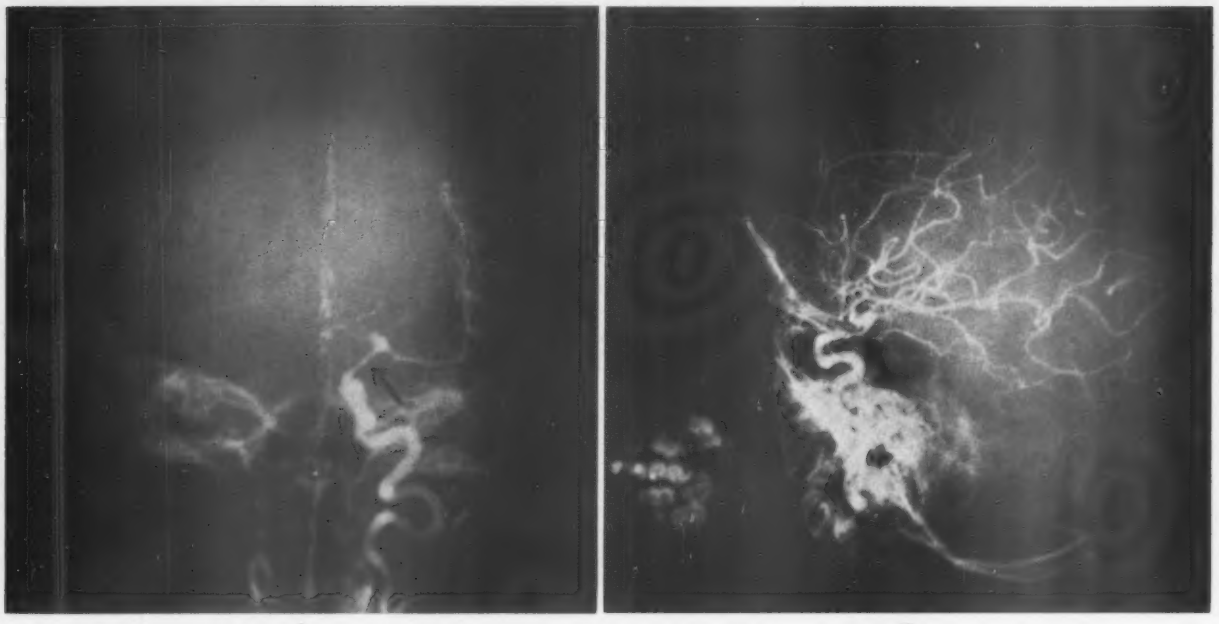


FIG. 2. Course under hypothermia.



A B

FIG. 3. Left carotid arteriogram. A, frontal projection showing an aneurysm at the level of the takeoff of the anterior cerebral, middle cerebral and posterior communicating arteries. There is spasm of the surrounding vessels. B, Lateral view demonstrating the aneurysm and associated narrowing of the distal portion of the carotid syphon which probably represents associated spasm.

chromic. Fresh and crenated red blood cells were seen, and the protein content of the fluid was 170 mg./100 ml.

Hypothermia: The deterioration in the patient's neurologic condition, the rising temperature and the continued presence of fresh red blood cells in the spinal fluid indicated that the patient was continuing to bleed from his initial hemorrhage, or that he had suffered a recurrent hemorrhage. For this reason hypothermia was instituted on the eighth hospital day (Fig. 2), and it was hoped that this measure would decrease cerebral edema, arterial spasm and cerebral anoxia as well as lower the systemic blood pressure. Refrigeration was carried out by means of a Thermorite hyper-hypothermic apparatus, a rubber mattress filled with a circulating current of alcohol and water which could be cooled or warmed to the desired temperature. The patient's extremities were covered with ice packs. Premedication was 100 mg. secobarbital (Seconal®) and 27.5 mg. promethazine (Phenergan®) intramuscularly. During the initial six hours of cooling the patient received 300 mg. secobarbital, 40 mg. promethazine, 100 mg. chlorpromazine (Thorazine®), and 35 mg. meperidine (Demerol®) intravenously in divided small doses. After a rectal temperature of 32°C. had been obtained, the child required only small doses of these drugs (100 mg. secobarbital and 10 mg. chlorpromazine) at six hour intervals to aid in maintaining a steady state. The hypothermic procedure was without incident, except for an initial marked shivering response, with an associated rise in blood pressure to 200/100. This reaction was readily overcome with suitable doses of the above mentioned drugs. Continuous rectal temperatures were recorded by a thermocouple unit, and rectal temperature was maintained between 32°C. and 33°C. for the ensuing forty-eight hour period.

On the ninth hospital day, with the patient still hypothermic, *bilateral carotid arteriography* was performed. This revealed an aneurysm located at the junction of the terminal portion of the left internal carotid artery and its branches, the left middle cerebral, the left anterior communicating artery and the left posterior communicating artery (Fig. 3). Simultaneous roentgenograms revealed the kidneys to be well outlined by the contrast material and to be of normal configuration.

Operative Procedure and Postoperative Course: It was believed that the coarctation should be corrected first, thus achieving a permanent normotensive state and making subsequent neurosurgical repair of the ruptured aneurysm a safer procedure. On the tenth hospital day a thoracotomy was performed under continued hypothermia. An 8 mm. length of narrowed aorta was noted immediately below the origin of the ductus arteriosus. The constricted area was resected and aortic continuity was restored by an end-to-end anastomosis. On pathologic examination, the coarcted portion of the aorta was hour-glass in configuration, and its lumen admitted a probe of 1 mm. in diameter A thickened, narrow ductus arteriosus opened into the aorta less than 1 mm. proximal to the coarctation. A filamentous

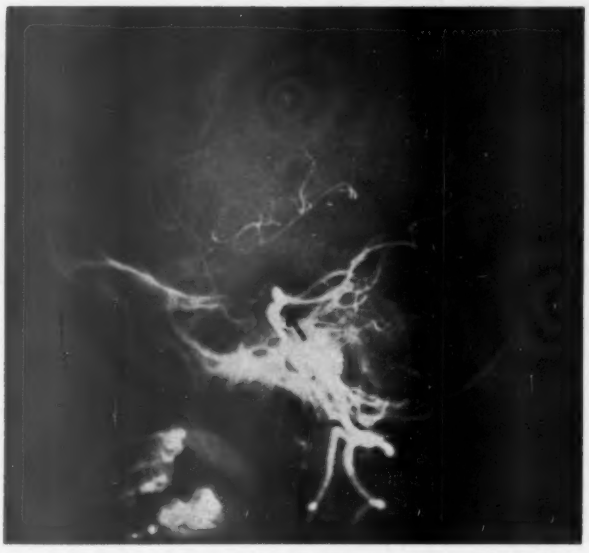


FIG. 4. Lateral view of vertebral arteriograms showing an additional aneurysm of one of the posterior cerebral arteries.

probe could be passed through the lumen of the ductus.

Hypothermia was discontinued immediately after surgery, and the postoperative period was uncomplicated. Blood pressure remained at normal levels (120/80 mm. Hg compared with a blood pressure of 156/100 mm. Hg on admission), and his neurologic status steadily improved. The only residual neurologic deficits were a left Horner's syndrome attributed to surgical trauma and dysesthesia and diminished vibration sense in the toes, which were probably due to the ice packs used in hypothermia or to previous ischemic changes.

Lumbar puncture ten days after surgery was normal and gradual ambulation was begun. Complete re-evaluation of the patient's status was planned with future neurosurgical intervention in mind. However, on the thirtieth hospital day the patient experienced a severe headache which was followed by a left-sided convulsion and subsequent coma. Physical examination revealed bilateral Babinski signs and generalized flaccidity. The blood pressure rose from 120/80 to 270/170 mm. Hg and respirations were slow and irregular.

Lumbar puncture disclosed grossly bloody spinal fluid with an initial pressure of 500 mm. Attempted carotid arteriography was unsuccessful, but a vertebral arteriogram demonstrated an aneurysm of one of the posterior cerebral arteries (Fig. 4). The patient died on the following day. Permission for postmortem examination was not obtained.

COMMENTS

REVIEW OF LITERATURE

Thirty-one autopsied cases of congenital intracranial aneurysms associated with coarctation of the aorta have been previously reported.[1–29] Our case and another have been proved by bilateral carotid arteriography.

Incidence: The incidence of congenital intracranial (berry) aneurysms associated with coarctation of the aorta has been reported to be 3.3 per cent, i.e., in ten cases among 304 coarctations proved by autopsy.[30,31] The incidence of berry aneurysms unassociated with coarctation has ranged from 0.65 to 1.1 per cent.[28] Congenital intracranial aneurysms have been reported to occur more frequently in women.[32] Chason and Hindman found the ratio of women to men to be 2:1 in their recent series.[33] However, men preponderate 4:1 or 5:1 among patients with coarctation of the aorta.[34] In the reported cases of congenital aneurysms associated with coarctation of the aorta, twenty-one patients were men and seven were women, a ratio of 3:1.

Age: The greatest incidence of berry aneurysms has been reported to occur in the third, fourth and fifth decades.[35] In two recent studies[33,36] the mean age of patients with ruptured aneurysms was fifty-four and forty-four. The mean age of those with unruptured aneurysms was sixty-four years. The range of ages in all the reported cases of berry aneurysms associated with coarctation of the aorta was from thirteen to seventy-seven years. The mean age of twenty-six patients with ruptured aneurysms was 28.6 years; the mean age of four with unruptured aneurysms was thirty-five years. The greatest number of ruptured aneurysms occurred in the second decade with a lesser but still considerable number occurring in the third decade. It would seem likely that the complicating factor of hypertension secondary to the coarctation was responsible for the earlier rupture.

Location: The location of aneurysms in this review corresponded to that of aneurysms in patients without coarctation.[28] Seventy-nine per cent were found in the carotid segment and 21 per cent were found in the vertebral segment of the circle of Willis. The greatest number of aneurysms was found in the middle cerebral, anterior cerebral and anterior communicating arteries.

There were 25 cases in which single aneurysms were present and ten cases in which multiple aneurysms were present, an incidence of multiplicity of about 30 per cent. This may be compared to the incidences of 11 to 31 per cent reported in studies of congenital aneurysms unassociated with coarctation.[33,35–37]

Mortality: Walton[29] reported the mortality from the initial episode of intracranial bleeding secondary to ruptured aneurysms to be 28 per cent. An additional 17 per cent of patients will die from recurrent hemorrhage within eight weeks after the initial bleeding episode.[38] A review of the autopsied cases in the literature showed the total number of ruptured aneurysms associated with coarctation in which the time sequence has been reported to be twenty-one. Death was secondary to the initial bleeding episode in twelve cases (57 per cent). Six patients suffered a recurrent fatal episode of bleeding within eight weeks (29 per cent); two had fatal recurrences later than eight weeks after the initial bleeding episode. Five additional patients died as a direct result of intracranial hemorrhage but the time sequence was unknown. Only one patient[27] with rupture of a proved cerebral aneurysm and associated coarctation had a complete recovery; the aneurysm was successfully repaired three years after the initial rupture. Four patients had unruptured aneurysms and died of other complications of coarctation of the aorta. It can be seen that 86 per cent of patients with ruptured cerebral aneurysms associated with coarctation had a fatal outcome within eight weeks of the initial rupture. This is in contrast to the better prognosis in patients without coarctation.[38]

Surgical Experience: Previous surgical experience in this problem has been limited. Tulloh[39] reported a case of a twenty-seven year old male with subarachnoid hemorrhage and coarctation of the aorta treated medically during the period of active intracranial bleeding with repair of the coarctation five months after the initial bleeding episode. Bigelow[25] reported a case similarly managed, but this patient sustained a fatal recurrent intracranial hemorrhage four weeks after repair of the coarctation.

PREOPERATIVE MANAGEMENT OF HYPERTENSION BY HYPOTHERMIA

Our patient was treated preoperatively by medical therapy including antihypertensive drugs and a period of controlled hypothermia. In patients with ruptured aneurysms without coarctation, a 20 per cent higher mortality has been reported[40] in those with coexistent hypertension than in normotensive individuals. Our review shows that 86 per cent of patients with ruptured intracranial aneurysms associated with coarctation succumbed within eight weeks compared with 57 per cent of patients with ruptured aneurysms unassociated with coarctation. Therefore, in treating a ruptured aneurysm associated with coarctation, it seems advisable to attempt to lower the arterial blood pressure. This may be achieved by the use of antihypertensive drugs or by the use of hypothermia with the body temperature maintained at safe levels of 30° to 32°c. Hypothermia has also been shown to diminish the oxygen requirements of the brain and to reduce cerebral edema and venous pressure.[41,42] Because of these additional beneficial effects, it would seem that the immediate induction of hypothermia is preferable to the use of antihypertensive drugs in the treatment of the acute phase of intracranial bleeding due to a ruptured aneurysm. A permanent normotensive state may usually be obtained by surgical correction of the coarctation. This operation is accompanied by a low mortality and morbidity at the present time.[43,44]

After the induction of hypothermia it is advisable to perform bilateral carotid arteriography as well as vertebral arteriography because of the high incidence of multiplicity of aneurysms. If multiple aneurysms are present, one must determine which aneurysm has ruptured. The clinical picture may aid in solving this problem. Also, in the absence of cerebral atherosclerosis, local vasospasm around the aneurysm is frequently an excellent angiographic sign that indicates the site of bleeding.[36] Such a sign was present in the left carotid arteriogram of our case.

SURGICAL INDICATIONS

The most perplexing problem in the treatment of ruptured intracranial aneurysms associated with coarctation of the aorta is whether it is wiser to repair the coarctation before or after attempting surgical correction of the aneurysm. In our case the neurosurgeons recommended that the coarctation be corrected first because hypertension increases the risk associated with neurosurgical intervention.[40] Even under hypothermia anesthesia, repair of a ruptured aneurysm during the phase of active intracranial bleeding is fraught with greater hazard than operation when the bleeding has subsided.[42] Our case demonstrated that the coarctation could be successfully repaired during the phase of acute intracranial bleeding, but the patient suffered a fatal recurrent hemorrhage before neurosurgical repair of the aneurysm was undertaken. One might postulate that perhaps the outcome might have been more favorable had neurosurgery been done

within one week after completion of thoracic surgery.

Other neurosurgeons believe that the aneurysm should be operated upon before the coarctation because the ruptured aneurysm, not the coarctation, is the immediate threat to life. Two problems confront the neurosurgeon: first, the treatment of the acute bleeding episode and second, the prevention of recurrent hemorrhage. Direct surgical repair of the aneurysm undertaken three weeks after the initial bleeding episode has been associated with a low mortality and morbidity (4 and 6 per cent, respectively, in a recent series), and grants permanent protection from recurrent hemorrhage.[45] Neurosurgery during the first week holds the additional promise of saving a number of those patients who would otherwise die from the effects of the initial rupture. Unfortunately, at the present time such immediate surgery is associated with a high mortality rate of approximately 23 per cent.[42] This rate is comparable to the mortality expected in such cases that have been left to run their natural course during this early period.[45,46] Cerebral edema, arterial spasm and intracerebral hematomas are factors which account for the high mortality of surgery performed in the acute period.[42] Perhaps a two to three day period of hypothermia preoperatively, judicious timing of intervention, and further refinements in surgical technic and anesthesia will reduce the present high mortality of surgery undertaken during the first week after the acute hemorrhage.

It is fortunate that the majority of aneurysms involve the carotid segment, for these are more accessible to surgery than those of the vertebral segment of the circle of Willis. Multiple aneurysms are not a contraindication to surgery, and bilateral staged aneurysm surgery has been successfully performed.[36]

We believe that a ruptured intracranial aneurysm associated with coarctation of the aorta should be treated by the immediate induction of hypothermia followed by bilateral carotid arteriography and vertebral arteriography. Neurosurgery should be undertaken no later than three weeks after the acute bleeding episode: and, if the patient's clinical condition permits, within one week of the initial hemorrhage. Hypothermia should be continued following repair of the aneurysm, and the coarctation should be corrected shortly thereafter. If the coarctation is corrected first, the aneurysm should be repaired no later than three days after thoracic surgery. It is entirely possible that both lesions could be corrected in one sitting. Suffice it to say that the time interval between the repair of both lesions should be no longer than four to five days.

Summary

A case is reported of a fourteen year old boy with coarctation of the aorta who suffered rupture of an intracranial aneurysm. The patient was treated by antihypertensive drugs, a period of controlled hypothermia and surgical correction of the coarctation during the period of active intracranial bleeding. To our knowledge this is the first case of this condition in which successful repair of the coarctation has been accomplished during the period of acute intracranial bleeding.

Thirty-two additional cases of intracranial aneurysm associated with coarctation have been reviewed. Rupture of the aneurysms occurred at an earlier age and was associated with a greater mortality rate than in aneurysms unassociated with coarctation.

Hypothermia, by reducing the arterial pressure and diminishing cerebral edema and anoxia, appears to be beneficial to these patients. Both carotid and vertebral arteriography should be performed because of the high incidence of multiple aneurysms. The question is discussed as to whether the coarctation should be repaired before the ruptured aneurysm or whether the aneurysm should be corrected first with subsequent repair of the coarctation. It is our belief that the latter is preferable. It must be emphasized that the time interval between the repair of both lesions should be extremely limited.

Acknowledgments

Grateful acknowledgment is made to Miss Kay Farrelly and to Mrs. Isabel Hall for their secretarial assistance, and to Mr. Henry C. Brunberg, Vice Consul of Finland, for his aid in translating several works in the Finnish literature. We also thank Dr. Horace L. Hodes, Chairman of the Dept. of Pediatrics, for his advice and excellent editorial comment.

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An Unusual Complication of Myocardial Infarction

Persistent Bigeminy Only in the Recumbent Position*

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THE DEVELOPMENT of a cardiac arrhythmia as a sequel to myocardial infarction is quite frequent. Most commonly one sees premature ventricular contractions and bigeminal rhythm may occur. However, persistent bigeminy in only the recumbent position in a patient having sustained a severe myocardial infarction, not receiving digitalis, seemed to us very unusual. We have been unable to find mention of this occurrence in the literature.[1,2]

CASE REPORTS

A. S., a forty-nine year old white electrician, was admitted to the Southampton Hospital on February 1, 1956, because of anterior chest pain of twenty-two hours' duration. His past health had been excellent and he had no previous cardiovascular symptoms.

Physical examination at the time of admission revealed the temperature 98.2°F., pulse 104 and regular, blood pressure 180/100 mm. Hg, respiration 18. The lungs were clear. The heart was slightly enlarged to percussion to the right and left. There were no thrills or murmurs.

Laboratory data showed a normal blood count and erythrocyte sedimentation rate of 21 mm./hr. Urinalysis was normal. The electrocardiogram showed an acute myocardial infarction of the posterior and anterolateral walls (Fig. 1).

Hospital Course: During the first twenty-four hours, opiates were required to control the chest pain which had become progressively more severe. There was a profound drop in his blood pressure so

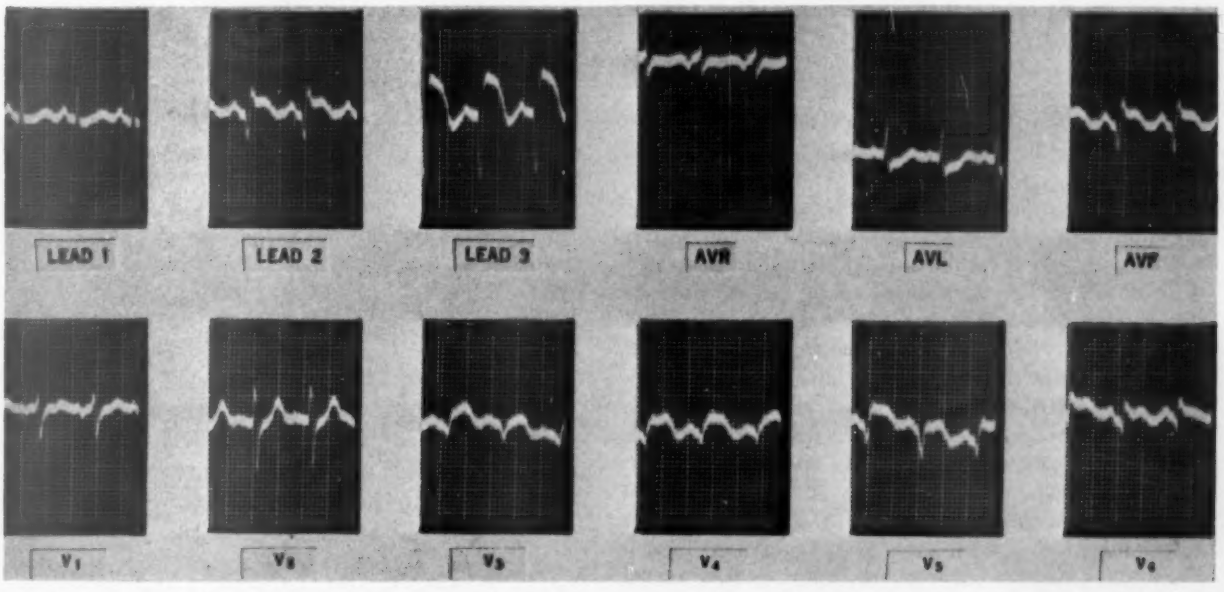

FIG. 1. Electrocardiogram on admission showing an acute myocardial infarction of the posterior and anterolateral walls.

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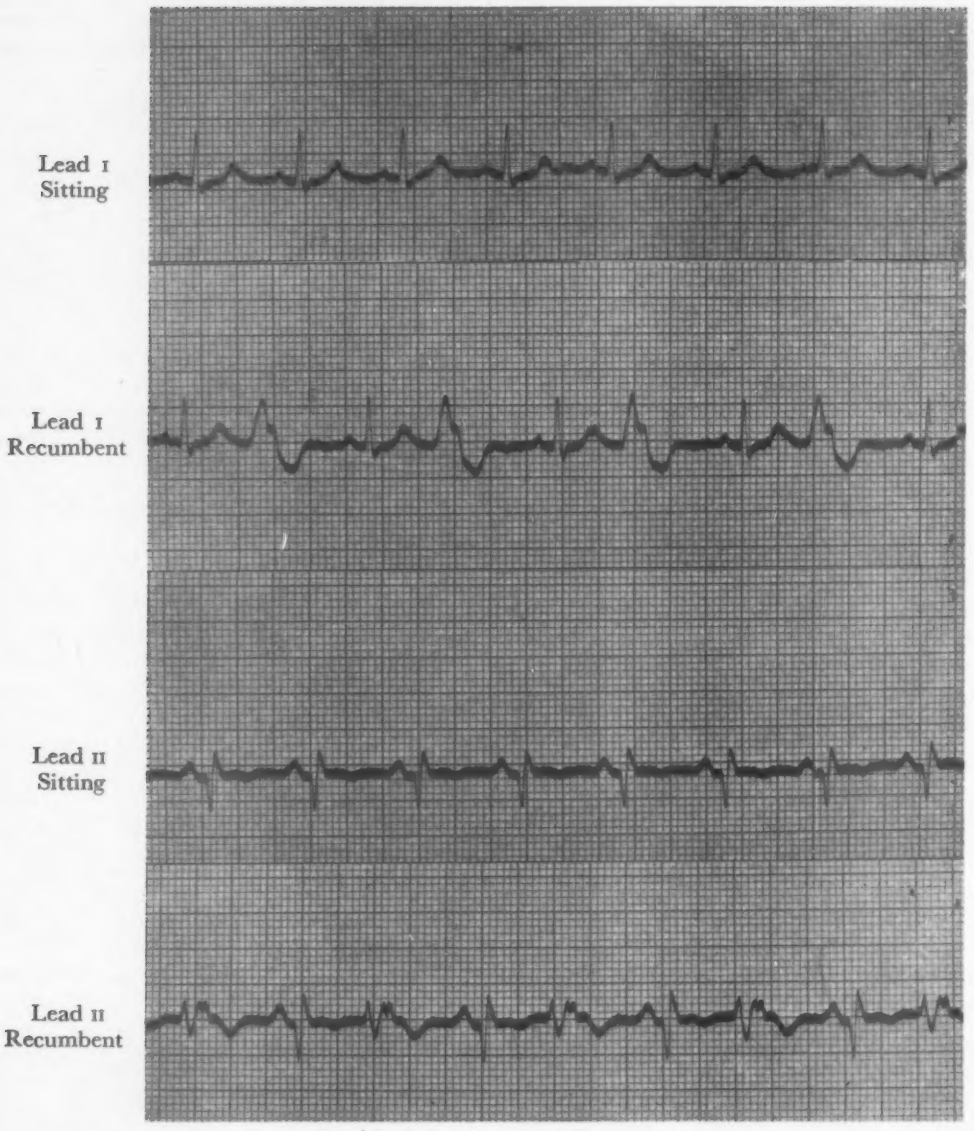

FIG. 2. Electrocardiogram taken January 1958 showing leads I and II in the sitting and recumbent positions.

that by twenty-four hours after admission it was unobtainable. His pulse became more rapid and weaker and he went into profound circulatory collapse. For the next twenty-four hours his condition remained critical. The shock was treated with plasma, hydrocortisone, norepinephrine, and Neo-synephrine® by intravenous infusion. Throughout this period a systolic gallop and a to-and-fro friction rub were audible. After this initial stormy period he responded to therapy and his condition steadily improved. For the first seventeen hospital days it was necessary, however, to use pressor drugs to maintain a satisfactory blood pressure. Serial electrocardiograms showed evolution of his extensive infarction.

Course Since Discharge: Since March 1956 he has had a bigeminal pulse in the recumbent position only (Fig. 2). This has not responded to sedatives, tranquilizers or quinidine. This bigeminy is present only when lying down and persists to date. He has returned to work and has been asymptomatic in all other respects.

COMMENT

There is no apparent explanation of this unusual phenomenon after a myocardial infarction, consisting of a bigeminal rhythm only in the recumbent position. There is perhaps an alteration in the coronary circulation in the recumbent position producing an irritable focus from which the ectopic beats originate. The patient first complained of palpitation when lying down. There has since been less awareness of this sensation. Despite a trial with adequate doses of quinidine, procaine

amide, sedation and tranquilizers there has been no change in the bigeminy.

Summary

A case is presented which demonstrated a previously unreported complication of myocardial infarction: persistent bigeminy only in the recumbent position. A forty-nine year old male had a severe myocardial infarction of the posterior and anterolateral walls. Since recovery he has had persistent bigeminy in only the recumbent position. This has not been altered by quinidine, procaine amide, tranquilizers or sedatives.

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Diagnostic Shelf

Aortic or Subaortic Stenosis?*

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HISTORY

A seventeen year old white boy was referred to the hospital in September 1959 because of mild dyspnea and "sticking" pain in the left side of the chest after strenuous exertion. There was no past history of rheumatic fever or hypertension.

In 1953 a systolic murmur at the base of the heart was noted for the first time. The boy remained asymptomatic until 1957 when, during a long, arduous hike, a sharp nonradiating pain developed under the left nipple. The systolic murmur was again heard and there was electrocardiographic evidence of left ventricular hypertrophy. Right heart catheterization revealed normal pressures and no evidence of a shunt. In the following two years the patient noted very mild dyspnea with extreme exertion. In April 1959, although there had been no significant progression of symptoms, the electrocardiographic pattern of left ventricular hypertrophy appeared to have progressed and there was inversion of the T waves. Left ventricular puncture was attempted but this procedure was technically unsatisfactory. In spite of the technical complications some of the left ventricular systolic pressures were considerably higher than those measured in the brachial artery. The lesion was diagnosed as aortic stenosis and in June 1959 correction of the stenosis was attempted at another hospital using cardiopulmonary bypass. Unfortunately, there was malfunction of the pump oxygenator and the heart was not opened, but pressures measured in the outflow tract of the left ventricle and in the aorta were equal. He was then referred to the Johns Hopkins Hospital for evaluation of a probable subaortic stenosis.

PHYSICAL EXAMINATION

Examination revealed a normally developed, slightly obese young man. The blood pressure was 130/60 mm. Hg and the pulse rate was 72/minute and regular. The apical impulse was prominent and thrusting. A loud systolic murmur of the ejection type was heard over the whole precordium and was best heard at the apex. It could be heard over the carotid arteries but its intensity was considerably diminished. There were no murmurs in diastole.

The electrocardiogram showed a normal axis, left ventricular hypertrophy and "strain." This pattern had progressed since 1957 with more striking inversion of the T waves in leads V_3 to V_6.

Roentgenograms revealed generalized cardiac enlargement. At fluoroscopy the left ventricle and left atrium were considerably enlarged and the right ventricle also was thought to be moderately enlarged.

CARDIAC CATHETERIZATION

The patient was submitted to retrograde left ventricular catheterization through the right brachial artery. The pressure in the aorta was 92/64 mm. Hg and in the left ventricular outflow tract it was 92/10 mm. Hg. The systolic pressure in the aorta and left ventricular outflow tract were thus equal. Proximal to this outflow area and about 4 cm. below the aortic valve, a ventricular chamber was entered which had a pressure of 170/10 mm. Hg and the systolic pressure was 60 to 80 mm. Hg higher than that in the outflow chamber (Fig. 1A and B). Repeated pullbacks across this area inside the ventricle demonstrated this systolic pressure gradient in every instance. The cardiac index

* From the Departments of Medicine and Surgery, The Johns Hopkins Hospital, Baltimore, Maryland. Aided by Grant H-226 from the National Heart Institute.

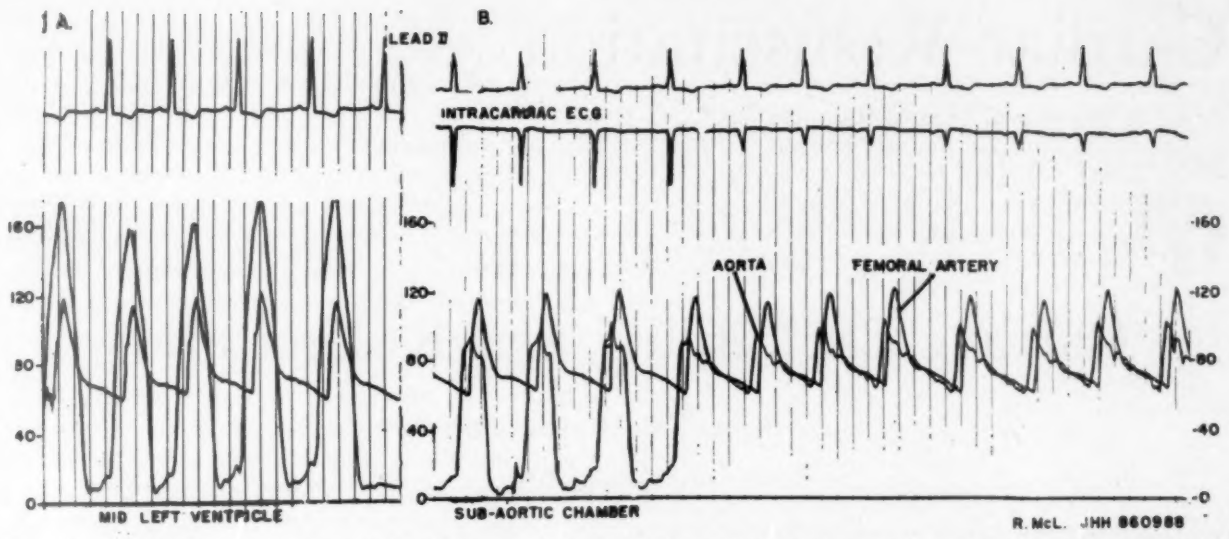

FIG. 1. A, simultaneous pressures in the femoral artery (120/60) and the "high pressure" mid-left ventricle (170/10) on equally sensitive strain gauges. The systolic pressure gradient may be seen between ventricle and femoral artery. B, pressures recorded in the "low pressure" subaortic ventricular chamber and the aorta as the catheter is pulled back across the aortic valve. Simultaneous femoral artery pressure is also shown. There is no systolic gradient across the aortic valve. A decrease in amplitude of the intracardiac electrocardiogram may be seen as the catheter tip crosses the aortic valve.

by the dye dilution method was 3.2 L./min./M²-BSA.

DIAGNOSIS

The final conclusion was that the patient had subaortic stenosis with an outflow chamber about 4 cm. long. Because of the generalized cardiomegaly and the atypical murmur and because the obstruction was so far inside the left ventricle (4 cm.), it was believed that this case probably represented a "functional" narrowing of the outflow tract of the left ventricle. These findings are quite similar to those in the cases described by Brock,[1] Bercu et al.[2] and Morrow and Braunwald.[3] Further surgery was not advised.

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Cardiac Resuscitation

Edited by PALUEL J. FLAGG, M.D., F.A.C.C.*
New York, New York

Cardiac Excitability and Resuscitation

ROBERT M. HOSLER, M.D.
Cleveland, Ohio

ONE OF SEVERAL inherent and overlapping properties of cardiac muscle is excitability. Another is the all or none law. This declares that the weakest effective stimulus will produce the maximum contraction. There is thus no proportionality between strength of stimulus and force of contraction. A stimulus is any environmental change that can evoke a reaction.

Both of these properties as well as many additional phenomena must be considered in order to comprehend fully the restoration of the heart beat. Nevertheless, the fundamental problem in cardiac resuscitation is to keep the brain viable.[1] The resuscitation procedure is thus divided into two separate and distinct chronologic steps: (1) the re-establishment of the oxygen system and (2) the restoration of the heart beat.

CARDIAC EXCITABILITY AND RESPONSE TO STIMULATION

Descriptions and explanations of this excitatory process are given almost entirely in terms of resistance, polarization, repolarization and others, which are referred to as electrical properties of the cell membrane. It seems that present knowledge of the metabolic process underlying excitability and the response to stimulation is still quite limited. The excitability of the heart does not remain constant. It changes as neural and humoral influences operate upon the heart as well as modifications during the cardiac cycle and during arrest.

The role of cellular metabolism markedly influences excitability. Upon contraction there is a breakdown of labile chemical substances followed by resynthesis. Unfortunately, oxygen as an essential component cannot be stored in the cells or tissues. With a lack of oxygen within a short lapse of time, incomplete microaerobic or anerobic metabolic reactions probably come into limited operation and these are quickly exhausted. Oxygen is one of the principal agents which has a profound influence on the permeability of the cell membrane and consequently upon the excitability period.

It would appear that considerable study has been carried out[2] pertaining to the effects of extracellular concentrations of ions (Ca and K), pH, temperature, drugs and others, which have a direct influence on an increase or decrease in excitability. It also appears that there has been a paucity of detailed investigation of the effects of hypoxia, hypercapnia and anoxia upon this important cardiac property, particularly at the onset of cardiac arrest.

Anoxia and Excitability: An arrested heart with its oxygen-depleted cardiac muscle will completely lose its excitability in the matter of a relatively short period of time. When this point is reached, the heart will not respond to a physical or natural stimulus and reaches absolute refractoriness although electrical activity remains which is usually indicated on the electrocardiogram. Rodeo and Porter[3] report that lack of oxygen is more important than lack of substrate in producing irreversible cardiac arrest. Anoxia has more effect on disrupting the permeability of the cell membrane than various ions and agents. This condition may also doubtlessly result in some intrinsic change.

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It is probable that the intrinsic excitatory process, which initiates a contraction of heart muscle, acts in the same manner as do applied stimuli.

Electrical monophasic stimulation of the anterior surface of the left ventricle[4] produces a reduction in threshold voltage during moderate hypoxia until severe hypoxia has its onset which is promptly followed by a rapidly rising threshold. Significant threshold changes occur at about 15 volumes per cent of oxygen. Below 6.4 volumes per cent of oxygen the threshold rises quickly and the conduction rate rapidly increases. In moderate hypoxia the functional capacity of the heart muscle is not impaired. Following stagnant anoxia for thirty to sixty seconds, a point can be reached where there is absolute refractoriness.

The previous significant facts are of singular importance in considering cardiac resuscitation, particularly in the restoration or initiation of the heart beat by physical stimulation, such as pounding upon the chest, the application of an external pacemaker stimulus or the employment of an external defibrillating shock.

After cessation of the coronary circulation the mammalian heart appears to lose the property of excitability within thirty to sixty seconds and rapid functional deterioration follows. Some means of reversing this process and restoring cellular metabolism must be provided after this time limit. Perfusion of the coronaries will adequately restore its chemical metabolic energy sources even after many minutes of arrest. At present there are two practical means for the accomplishment of this:[5] (1) manual cardiac massage and (2) intra-arterial transfusion under pressure.

Drawbacks of Closed Chest Resuscitation

Observation of a great many hearts in our laboratory which have been deliberately arrested by weak currents and thus placed in a state of ventricular fibrillation indicates that cyanosis can be detected by the naked eye within seven seconds after its onset. After the lapse of thirty seconds the heart is markedly blue yet the blood trapped in the main coronary arteries remains bright red.

External Defibrillation: Accomplishment of external defibrillation in animals has been successful for many years. Nevertheless, it has not proved practical in restoring circulation to an arrested fibrillating heart after forty-five to fifty-five seconds' duration of such an arrhythmia. Failure occurs not from the inability to accomplish defibrillation of the heart, but from the inability to restore a blood pressure compatible with life. Electrocardiographic evidence is readily obtained which indicates that the heart has been defibrillated (Table I). However, after one minute a pulse or a systemic blood pressure is seldom recordable; and upon promptly opening the thorax, one will find the heart in a state of standstill or asystole. In the meantime the heart is dying although acceptable complexes are recorded upon the electronic monitor. It is clear that electrical activity as recorded by the electrocardiograph is not necessarily related to the effectiveness of the circulation.[6] However, most of us are reluctant to accept the fact that electrical activity can persist long after mechanical activity has ceased.

Table I
Closed Chest Defibrillation

Experiments (no.)	Duration of Fibrillation (sec.)	Defibrillation in Electrocardiogram	Return of Blood Pressure and Pulse	Open Chest Massage	Normal Circulation Restored
1	15	+	1	0	1
1	25	+	1	0	1
4	30	+	4	0	4
4	35	+	3	1	4
8	45	+	3	5	8
5	55	+	2	2	4
5	60	+	2	3	5
13	65	+	1	12	13
*12	70	+	0	*12	12
11	75	+	3	8	11
2	85	+	0	0	—
6	90	+	0	4	4
2	120	+	0	1	1

* Pacemaker stimulation applied to eight dogs in the seventy second group (before massage) without success.

Experimental Closed Chest Resuscitation: We have carried out many animal experiments based upon restarting arrested hearts which are intimately associated with the practical time limit of the excitability of cardiac muscle. These experiments are summarized in Tables I to IV.

As indicated in Table I, somewhere around fifty seconds is the dividing line between satisfactory and unsatisfactory defibrillation by the external application of countershock in these experiments. This is in general agreement with Dow and Wiggers' report[7] in 1940. Beyond this point it was found that the heart could always be defibrillated as indicated by the electrocardiogram (Tables I and III), but there was seldom return of a satisfactory blood

TABLE II
Electrodes Applied Directly to Myocardium

No. of Dogs	Duration of Fibrillation (sec.)	Ventilation and Massage	Defibrillation in Electrocardiogram after Massage	Return of Circulation
86	120	86	86	86

TABLE III
Electrodes Applied Directly to Myocardium

No. of Dogs	Duration of Fibrillation (sec.)	Defibrillation in Electrocardiogram before Massage	Return of Circulation	Open Chest Massage	Return to Normal Blood Pressure
70	120	70	0	70	70

TABLE IV
External Defibrillation and Supplemental Methods

Dog Experiments (no.)	Duration of Fibrillation (sec.)	Arterial Perfusion after (sec.)	Total Arrest of Circulation (sec.)	Return of Circulation
3	45	0	45	+
1	55	0	55	+
2	65	120	120	+
1	65	125	125	+
3	75	150	150	+
2	85	150	150	+
1	90	150	150	+
1	105	180	—	0
1	120	180	180	+

pressure or pulse. In this situation it was found that rapid surgical exposure of the heart, followed by a short manual pumping of that organ, readily and successfully restored the heart beat, blood pressure and the circulation to a normal level. In other experiments[8] (Table IV), after electrical defibrillation had been recorded and no return of systemic circulation occurred within 120 to 150 seconds, the administration of an intra-arterial infusion of saline and 1:10,000 dilution of adrenalin under pressure of 300 mm. Hg resulted in a satisfactory return of systemic circulation without opening the chest.

Mammalian hearts arrested for sixty to 120 seconds lose their excitability and ability to respond to a stimulus (Tables I and III). Supplemental methods for restoring the cellular metabolism must be employed. During the past twenty years we have empirically recommended for successful defibrillation that the myocardium be pink and well oxygenated before applying a shock with internal electrodes (compare Tables II and III).

Another problem in closed chest defibrillation is that of obtaining a current flow of sufficient density in all parts of the cardiac musculature. The anatomy of the organs of the thorax and mediastinum does not lend itself to constant degrees of tissue conduction and resistance.

CONCLUSIONS

There is a complex relationship between the cellular metabolic processes and the recovery of excitability which is initiated as soon as an adequate coronary circulation or perfusion is resumed or instituted. The heart as a muscular organ will remain viable as long as sixty to one hundred minutes; but in order for it to function as an hydrodynamic pump, it must have oxygenated blood circulated in its coronary system under an adequate pressure.*

To prevent death before it occurs and to reverse clinical death after it occurs is perhaps the most important problem at this time in the twentieth century. As of today, resuscitation is still in its infancy. The unpleasant and forbidding task of opening the chest remains the surest means of reversing clinical death. Other reliable and acceptable methods are universally being sought. To initiate successfully a heart beat by a physical stimulus alone, this stimulus must be applied or delivered before the period of excitation of the anoxic cardiac muscle cells has been terminated. This vital period is less than one minute.

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* This is presumed to be 40 mm. Hg as a minimum.

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Vector Leads*

RECENT interest in vectorcardiography has stimulated the study of electrocardiograms taken from the points of electrode placement for the vectorcardiogram. These leads have been called A,B,C leads[1] or X,Y,Z leads.[2] However, a better term for such leads is *vector leads* because they represent vectorcardiograms and show the direction of the electrical axis very clearly.

For example, a vectorcardiogram actually records the resultant of two simultaneous electrocardiograms taken from points which lie at right angles to each other and are equidistant from the center of the electrical battery of the heart.[3] Thus, in order to take a frontal plane vectorcardiogram, it is necessary to have two leads on the frontal plane, one lying horizontally (X lead), the other lying vertically (Y lead) (Fig. 1A). In order to take a horizontal plane vectorcardiogram, it is necessary to have two leads on the horiontal plane of the body, one lead lying horizontally (X lead), the other lying at right angles to this in an anteroposterior direction (Z lead) (Fig. 1B). In order to take a sagittal plane vectorcardiogram, it is necessary to have two leads lying on the sagittal plane, one lying horizontally in an anteroposterior direction (Z lead), the other (Y lead) lying vertically at right angles to lead Z (Fig. 1C).

Methods of Electrode Placement: The vector leads depend on the systems of vectorcardiography being used. There are two common methods of electrode placement. One is based on the Duchosal cube system[4] (Fig. 2), the other on the Wilson equilateral tetrahedron, which has one of its apices pointing backward[5] (Fig. 3A). The cube system of vectorcardiography requires placing electrodes on the patient's back (Fig. 2). The equilateral tetrahedron system uses leads I and aVF, but requires one lead, VB, to be placed on the back (Fig. 3A). Therefore, if one is interested in studying vector leads on the basis of these systems, it is necessary to take special leads in addition to those used for routine electrocardiography.

However, an equilateral tetrahedron with one apex pointing forward instead of backward can be used to obtain vector leads (Fig. 3B). When this is done, one can use leads I, aVF and V_1 as vector leads. Lead V_1 can be substituted for lead VB for the following reason: any two leads separated by an angle of 180 degrees show the same magnitude but opposite polarity.[6] Lead VB is taken on the back just to the left of the spinal process of the seventh thoracic vertebra. This lies at the level of the fourth rib anteriorly; and a point from VB passing through the center of the chest will pass through lead V_1. Leads VB and V_1 are therefore separated by an angle of 180 degrees and should show deflections of equal magnitude but of opposite polarity. (Since the heart lies somewhat anterior to the center of the chest, the potentials of lead V_1 will be somewhat greater than the potentials of lead VB. However, since we are using vector analysis, the directions and time relations of the deflections, and not their magnitude, are important.)

Polarity of Vector Leads: These vector leads show the direction of the electrical axis in the following ways:

Lead I shows the direction of the electrical axis on the frontal plane of the body. A downward deflection indicates movement of the electrical axis to the right. An upward deflection indicates movement to the left (Fig. 4).

* A contribution of the Dr. Louis B. and Anna H. Goldberger Memorial Foundation for Medical Research.

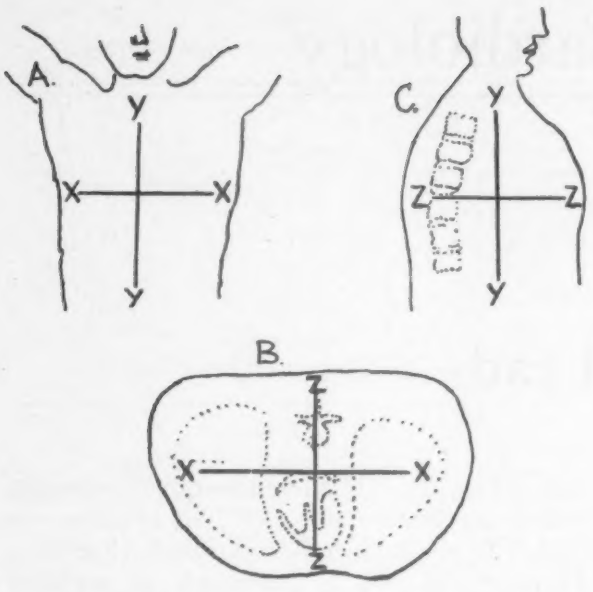

FIG. 1. A, the frontal plane of the body. B, the horizontal plane. C, the sagittal plane.

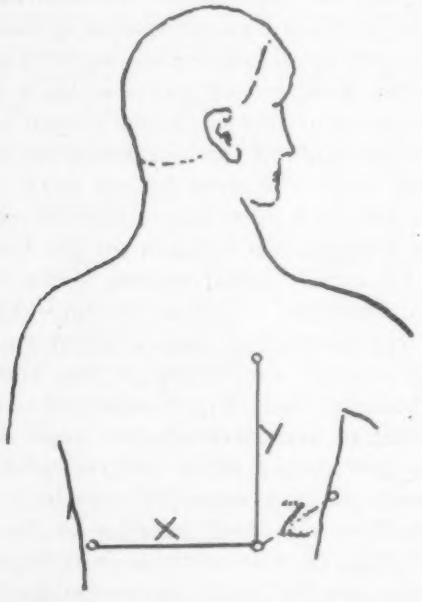

FIG. 2. The cube method of electrode placement.

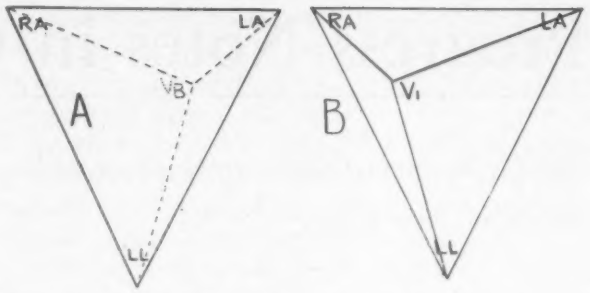

FIG. 3. A, Wilson's equilateral tetrahedron with one apex pointing backward. B, the author's equilateral tetrahedron with one apex pointing forward.

Lead V_1 shows the direction of the electrical axis on the horizontal plane of the body. A downward deflection indicates a posterior movement of the electrical axis. An upward deflection indicates an anterior movement (Fig. 4).

Lead aVF shows the direction of the electrical axis on the sagittal plane of the body. A downward deflection indicates a superior movement of the electrical axis. An upward deflection indicates an inferior movement (Fig. 4).

Applications of Vector Leads: Freibrun, Isaacs and Griffith[2] and I[3,7] have indicated some of the measurements which can be made with vector leads. For example, left bundle branch block can be differentiated from left ventricular hypertrophy with vector leads. In such a case of left ventricular hypertrophy, lead I shows a qR and lead V_1 shows an rS or QS. The initial q in lead I indicates movement of the stimulus to the right. The initial r in lead V_1 indicates an initial anterior movement of the stimulus on the horizontal plane. In other words, in left ventricular hypertrophy, the initial spread of the stimulus through the septum is to the right and anteriorly (rarely posteriorly). This indicates normal conduction through the ventricular septum.

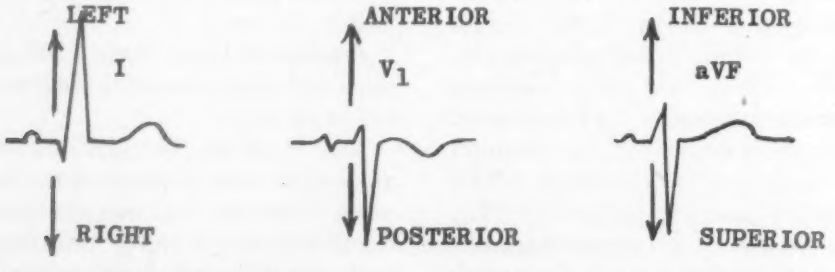

FIG. 4. Vector leads showing the relations between electrocardiographic deflections and the direction of the electrical axis.

However, in such a case of left bundle branch block, lead I will show a tall, slurred R, and lead V_1 a QS. The initial R in lead I indicates movement of the stimulus through the ventricular septum from right to left. The initial Q in lead V_1 indicates an initial posterior movement of the stimulus on the horizontal plane. In other words, in left bundle branch block, the initial spread of the stimulus through the ventricular septum is to the left and posteriorly (backward). This is characteristic of left bundle branch block.

Further studies of the usefulness of vector leads are worth while. However, I should like to suggest that whenever possible, two vector leads be recorded simultaneously (with a two-channel electrocardiograph) and with a paper speed of at least 50 mm./second so that accurate measurements of the vector sequences can be made.[7]

Also, in comparing vector leads taken with different methods, one should be careful to recognize differences due merely to reversal of polarity. For example, in Freibrun's paper,[2] lead X resembles lead I, lead Z resembles lead V_1, but lead Y is the opposite of lead aVF because it is taken with reversed polarity.

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College News

President's Column

LAST SUMMER as I watched the Democratic and Republican conventions, I again became aware of the size of the United States. It made me realize how important it is that our College be represented in all parts of the country. As a beginning toward reaching this goal, I sent a letter to the Trustees and Governors of the College stating that one of my objectives as President this year would be to balance the state-wide representation of membership in our College.

The Executive Director devised a map which graphically illustrates the College membership in each state as it now stands (Fig. 1). It is quite natural that numerically our largest membership grouping is in the East where the College started and where the concentration of doctors is greatest; but what immediately became evident is that certain areas are very sparsely represented, and the states of Wyoming and Utah are not represented at all. This summer the Executive Director made a personal visit to both Wyoming and Utah in order to interest the leading cardiologists in these two states in the work that the College is doing.

It is evident to all of us that there are many

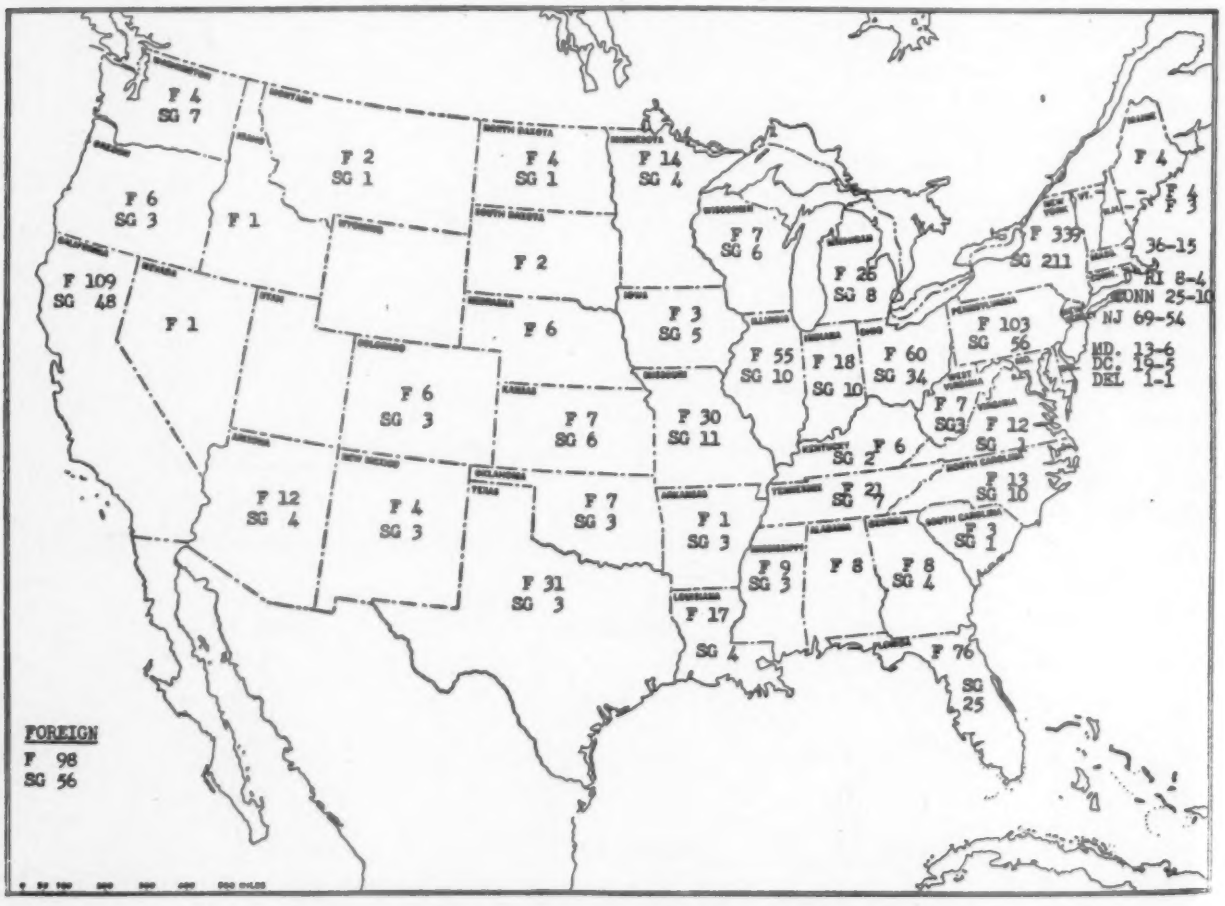


FIG. 1. Graphic illustration of College membership.

fine investigators and competent clinical cardiologists doing important work far removed from the great metropolitan centers. It is these men in the southwest, in the central plains and in the great northwest whom we must find and bring into our College. If we are thinly represented in those areas, it is not because the men are not there but because we have been lax in telling about the work we are doing, about why they should help us in this work and of how we can help them.

One of the ways that our membership can be built up is through regional conferences, set up under the auspices of the local Governors. Such regional conferences afford an opportunity for College members to get together and discuss some subject or some local cardiologic project in which they are particularly interested. Such informal conferences give the local groups a chance to know each other better; also other cardiologists in the area may learn something about what the College is doing.

I am very happy to say that a number of these regional conferences are being planned for the coming year.

The job of attracting qualified men is not just the work of Trustees and Governors. It should be carried on by all members of the College.

LOUIS F. BISHOP, M.D.

1961 Workshop Program

THIS year's program is limited to a selected schedule of six important workshops which are believed to be particularly attractive to members of the College.

Members of the College are urged to take advantage of this opportunity offered by your Postgraduate Education Committee by communicating with Dr. Philip Reichert, Executive Secretary, 350 Fifth Ave., New York 1, New York, relative to arrangements for participation. Due to the limited number of participants for each workshop, early registration is advised.

Clinical Workshop Program 1961

Date (1961)	Preceptor	Topic	Place	Maximum No. of Participants
January 11, 12, 13	Dr. Dwight E. Harken and associates*	Cardiology: clinical, hemodynamic, electrolyte, chemical and surgical survey	Amphitheater of The Peter Bent Brigham Hospital, Boston, Mass.	30
January 14	Drs. David Littman and Arthur Sasahara	Coronary angiography	Veterans Administration Hospital, West Roxbury 32, Mass.	30
January 21, 22 April and May	Dr. E. Sterling Nichol and associates	Acute and life-long anticoagulant therapy routines; care of acute and chronic nonsurgical cardiac problems	Miami Heart Institute, Miami Beach, Fla.	3
March 6	Dr. Louis F. Bishop	Office cardiology	141 East 55th St., New York 22, N. Y.	2
March 30, 31	Dr. Samuel Bellet and associates	Fibrinolysin, cardiac arrhythmias and cardiac catheterization	Heart Station, Philadelphia General Hospital, Philadelphia, Pa.	4
May 2	Dr. Don L. Fisher and associates	Left and right heart catheterization	Cardiopulmonary Laboratory, Allegheny General Hospital, Pittsburgh, Pa.	2

* The following preceptors, in addition to Dr. Harken, will collaborate in this workshop: Samuel A. Levine, M.D., Lewis Dexter, M.D., Laurence B. Ellis, M.D., Richard Gorlin, M.D., Francis D. Moore, M.D., Harold D. Levine, M.D., Bernard Lown, M.D., Warren J. Taylor, M.D. and Armand A. Lefemine, M.D.

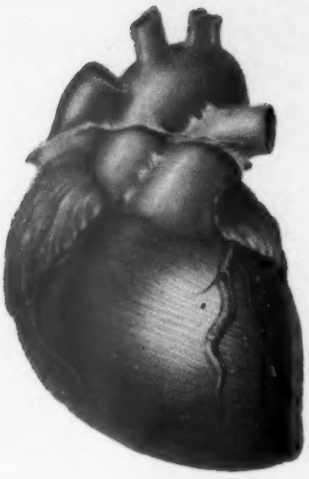
Col. Byron E. Pollock Retires from Fitzsimons

COL. BYRON E. POLLOCK, Chief of the Department of Medicine at Fitzsimons General Hospital, received his first Oak Leaf Cluster for his Army Commendation Medal and was officially cited at retirement ceremonies earlier this month at Fitzsimons.

Colonel Pollock was cited for his service both as chief of the Cardiology Service from January 30, 1955, and from August 1958 as chief of the Department of Medicine. From September 24 to November 11, 1955, Colonel Pollock was called upon to treat President Dwight D. Eisenhower for an acute cardiac illness at Fitzsimons General Hospital.

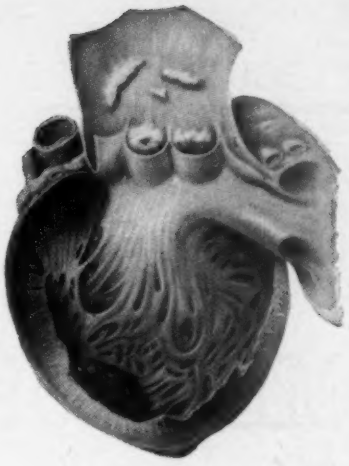
Col. Pollock has been active in the affairs of the College and at present is a member of the Board of Trustees. Since his retirement he has become Chief of Medicine at Denver General Hospital.

Maj. Gen. John F. Bohlender, Commander at Fitzsimons General Hospital presents the First Oak Leaf Cluster to the Army Commendation Medal and retirement citations to Col. Byron E. Pollock, MC, retiring chief of the Department of Medicine. (U. S. Army Photograph.)



IN ANGINA PECTORIS AND CORONARY INSUFFICIENCY

. . . the treatment must go further than vasodilation alone. It should also control the patient's ever-present anxiety about his condition, since anxiety itself may bring on further attacks.



AFTER MYOCARDIAL INFARCTION

. . . it is frequently not enough to boost blood flow through arterial offshoots and establish new circulation. The disabling fear and anxiety that invariably accompany the condition must be reduced, or the patient may become a chronic invalid.

Protects your coronary patient better than vasodilation alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, considerably delay recovery.

This is why Miltrate gives better protection for the heart than vasodilation alone in coronary insufficiency, angina pectoris and postmyocardial infarction. Miltrate contains not only PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. What is more important – Miltrate provides Miltown, a tranquilizer of *proven* effectiveness in relieving anxieties, fear and day-to-day tension in over 600 clinical studies.

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Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

REFERENCES

1. Ellis, L. B. *et al.*: Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J. E. F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.*: Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

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while more time is needed to determine the over-all prognostic significance, it has been observed that MER/29 "... reduced morbidity and mortality rates below those of control series during the first year following coronary thrombosis."[4]

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References: 1. Hollander, W., and Chobanian, A. V.: Boston M. Quart. *10*:37 (June) 1959. 2. Oaks, W., and Lisan, P.: Fed. Proc. *18*:428 (Mar.) 1959. 3. Oaks, W. W., *et al.*: A. M. A. Arch. Int. Med. *104*:527 (Oct.) 1959. 4. Lisan, P.: Proceedings, Conference on MER/29, Progr. Cardiovasc. Dis. *2*:(Suppl.)618 (May) 1960. 5. Oaks, W. W.: *Ibid.*, p. 612. 6. Hollander, W., *et al.*: *Ibid.*, p. 637. 7. Halperin, M. H.: *Ibid.*, p. 631. 8. Toro, J.: *Ibid.*, p. 544. 9. Morrison, L. M.: J.A.M.A. *173*:884 (June 25) 1960.

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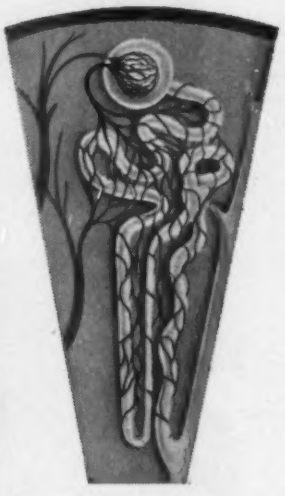

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***Fuchs, M.: A review of the thiazide pharmacology, Paper presented at Puerto Rican M. Soc., San Juan, Puerto Rico, Jan., 1960.**

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Recommended Daily Dietary Allowances and the Nutritional Contribution of a Basic Cereal and Milk Moderate Low-Fat Breakfast*

Menu: Orange Juice—4 oz.;
Cereal, dry weight—1 oz.;
Whole Milk—4 oz.; Sugar—1 teaspoon;
Toast (white, enriched)—2 slices;
Butter—5 gm. (about 1 teaspoon);
Nonfat Milk—8 oz.

Nutrients	Calories	Protein	Calcium	Iron	Vitamin A	Thiamine	Riboflavin	Niacin equiv.	Ascorbic Acid
Totals supplied by Basic Breakfast	503	20.9 gm.	0.532 gm.	2.7 mg.	588 I.U.	0.46 mg.	0.80 mg.	7.36 mg.	65.5 mg.
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Percentage Contributed by Basic Breakfast	19.3%	26.1%	40.9%	18.0%	11.8%	35.4%	40.0%	43.3%	81.9%

Cereal Institute, Inc.: Breakfast Source Book. Chicago: Cereal Institute, Inc., 1959.
Food & Nutrition Bd.: Recommended Dietary Allowances, Revised 1958. Natl. Acad. Sci.—Natl. Research Council Publication 589, 1958.
Watt, B. K., and Merrill, A. L.: Composition of Foods—Raw, Processed, Prepared. U.S.D.A. Agriculture Handbook No. 8, 1950.

**The allowance levels are intended to cover individual variations among most normal persons as they live in the United States under usual environmental stresses. Calorie allowances apply to individuals usually engaged in moderate physical activity. For office workers or others in sedentary occupations they are excessive. Adjustments must be made for variations in body size, age, physical activity, and environmental temperature.*

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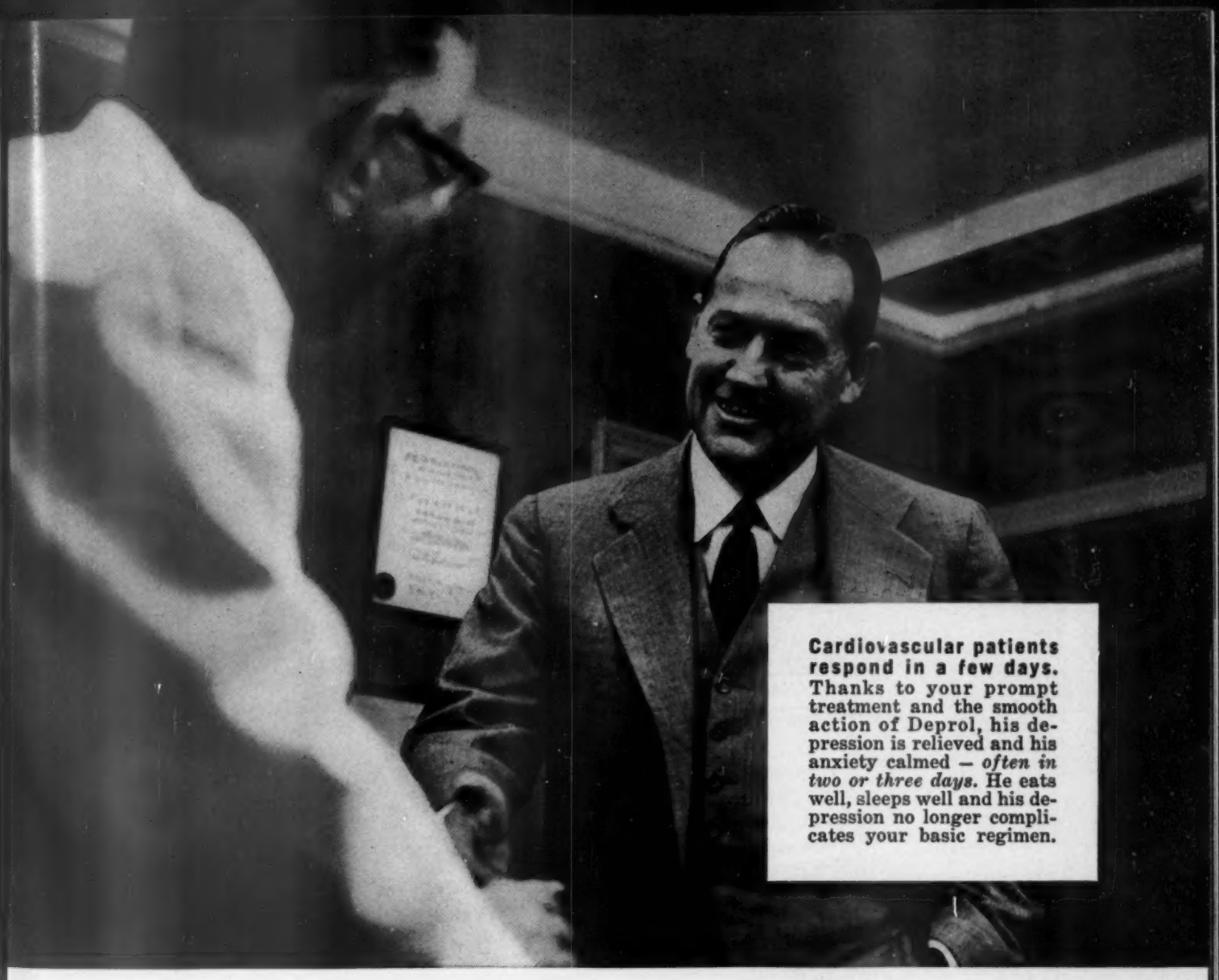

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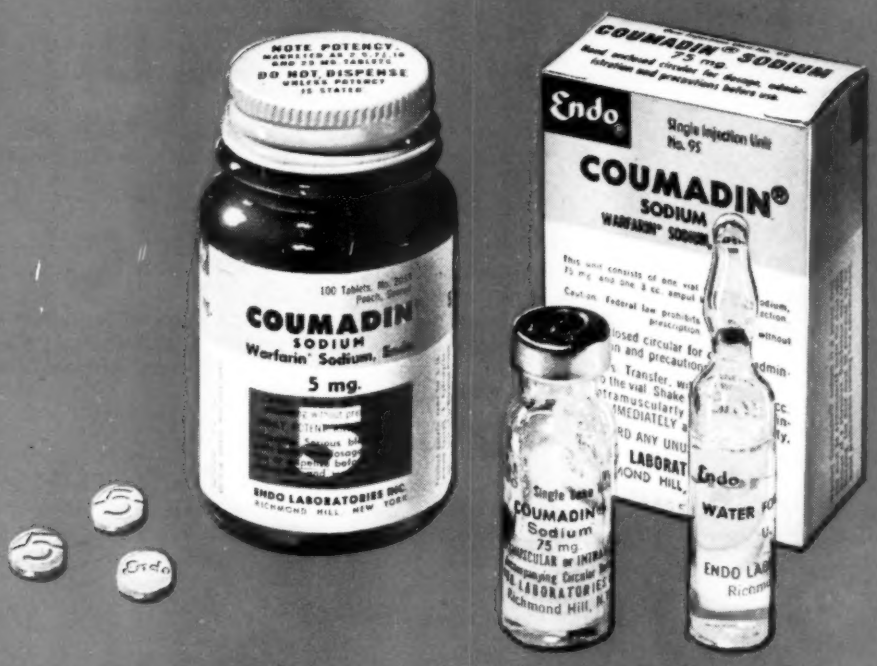

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1. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958. 2. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pubs., Mar., 1960, p. 13.

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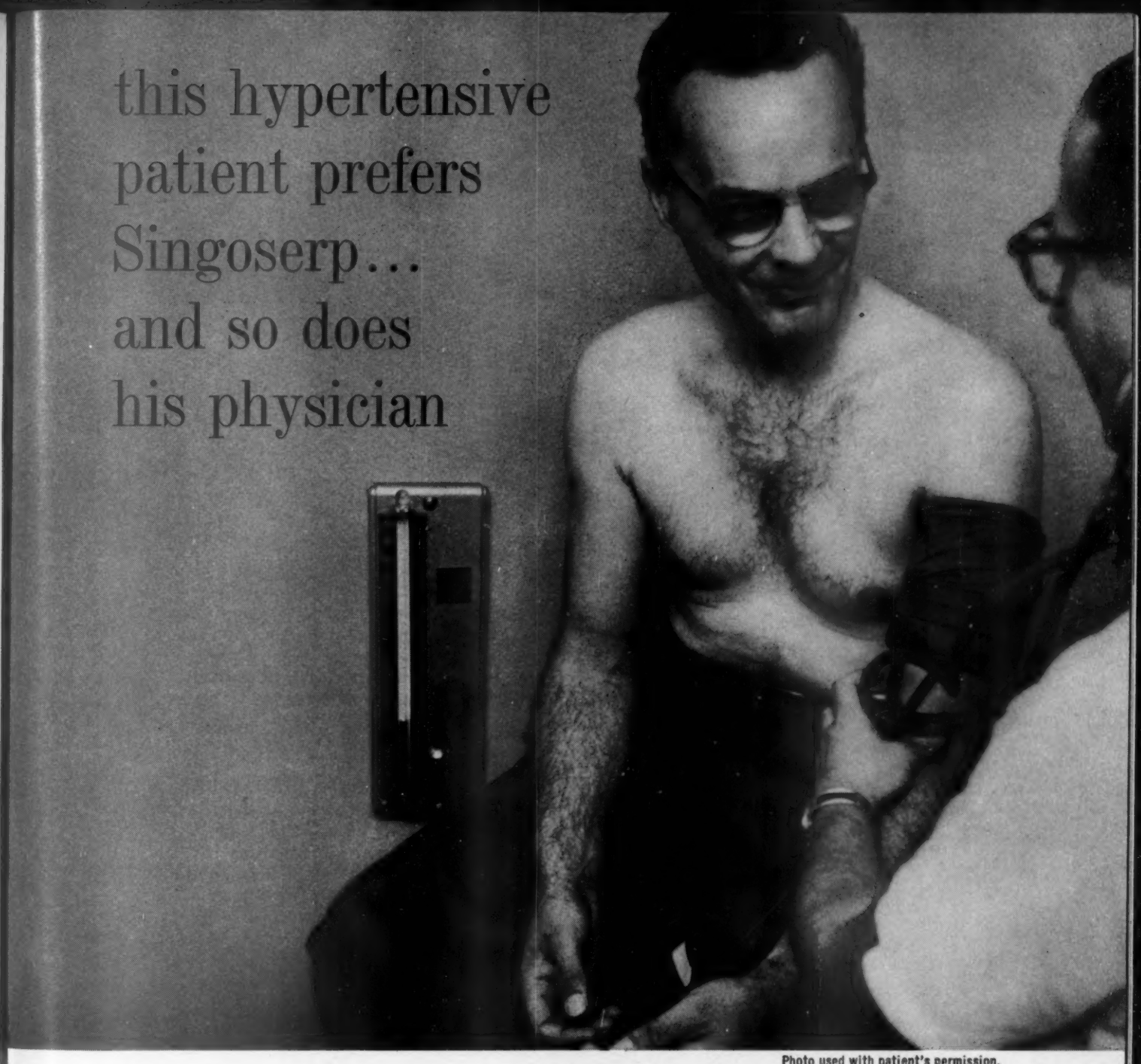

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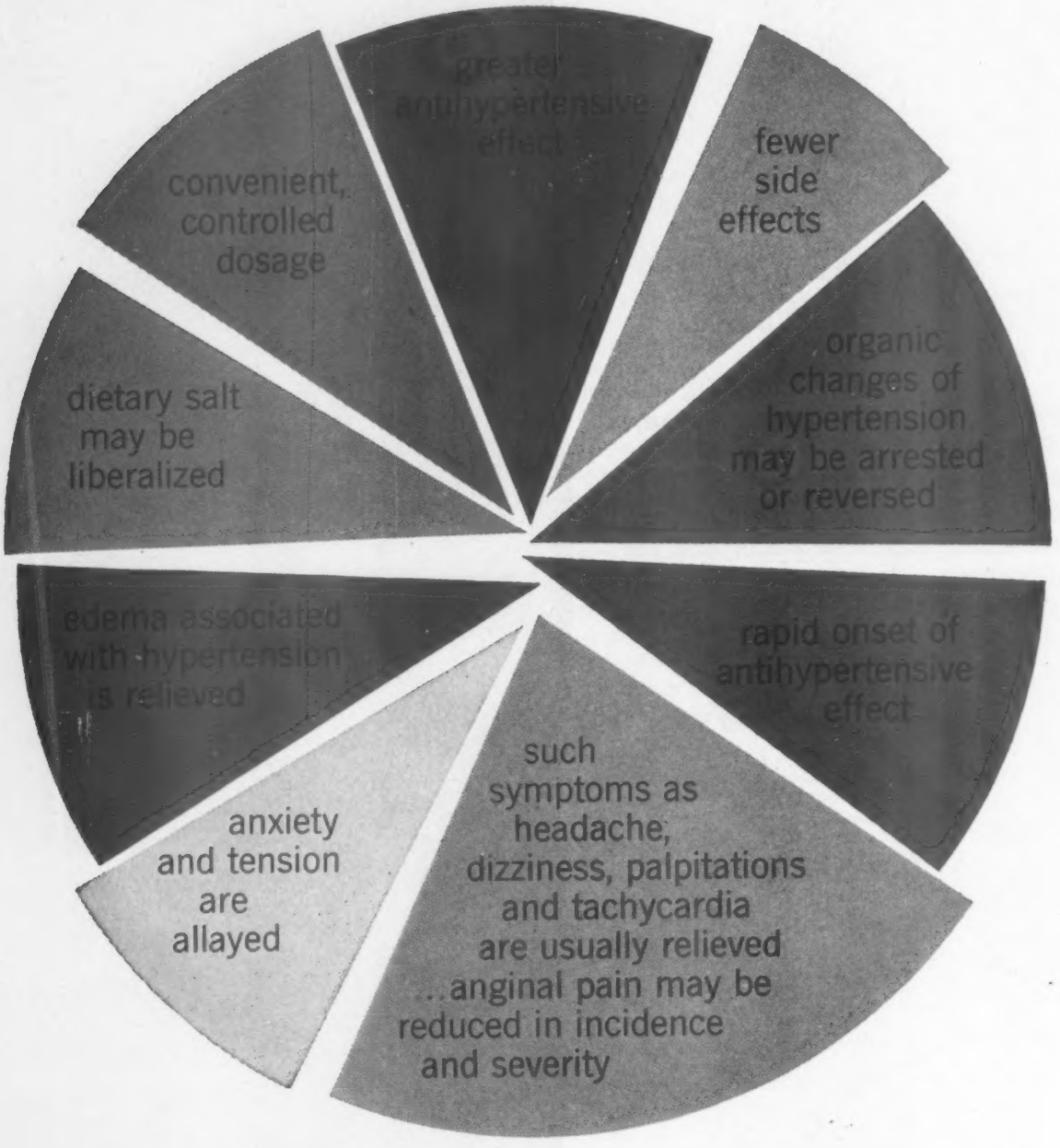

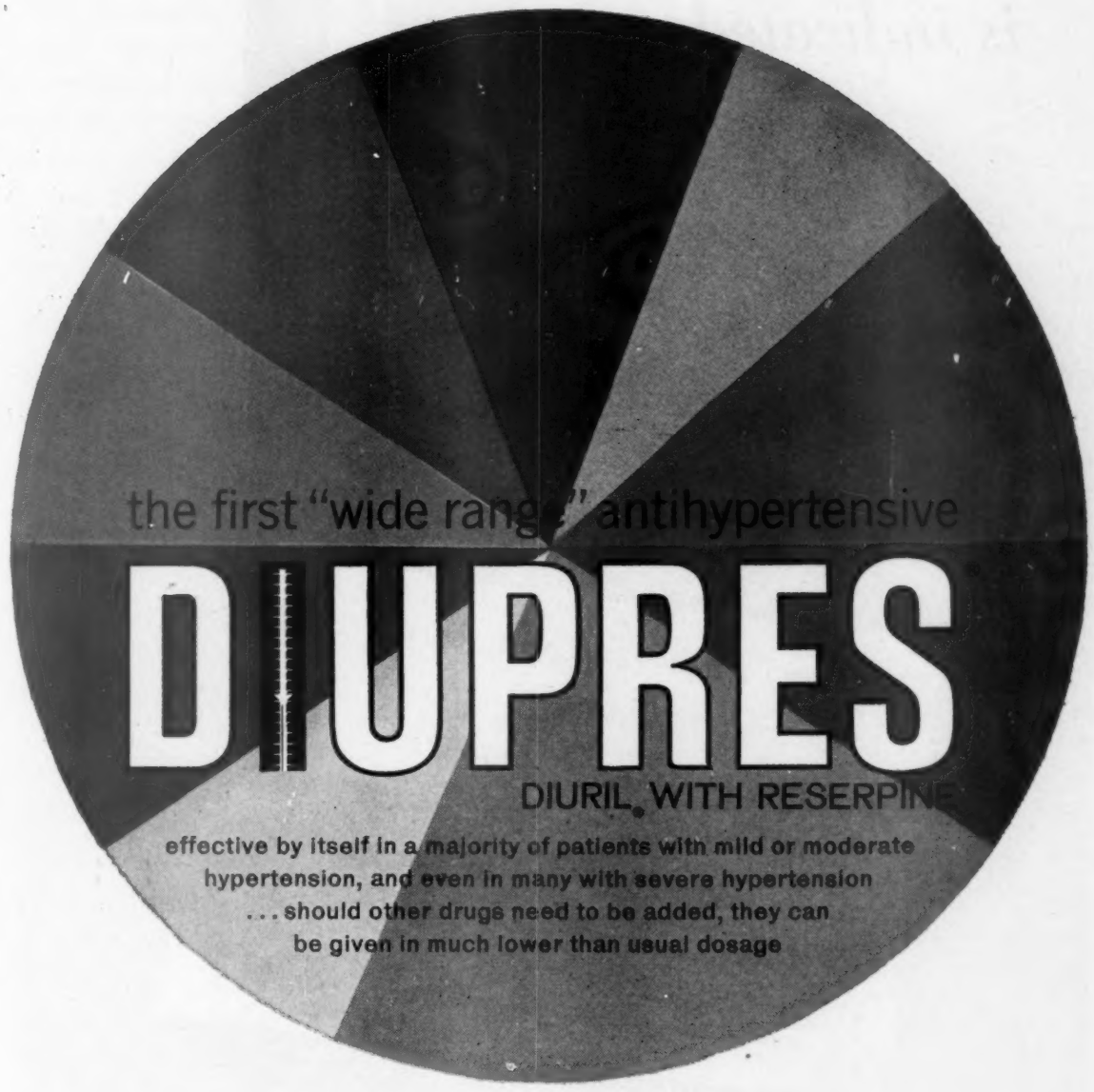

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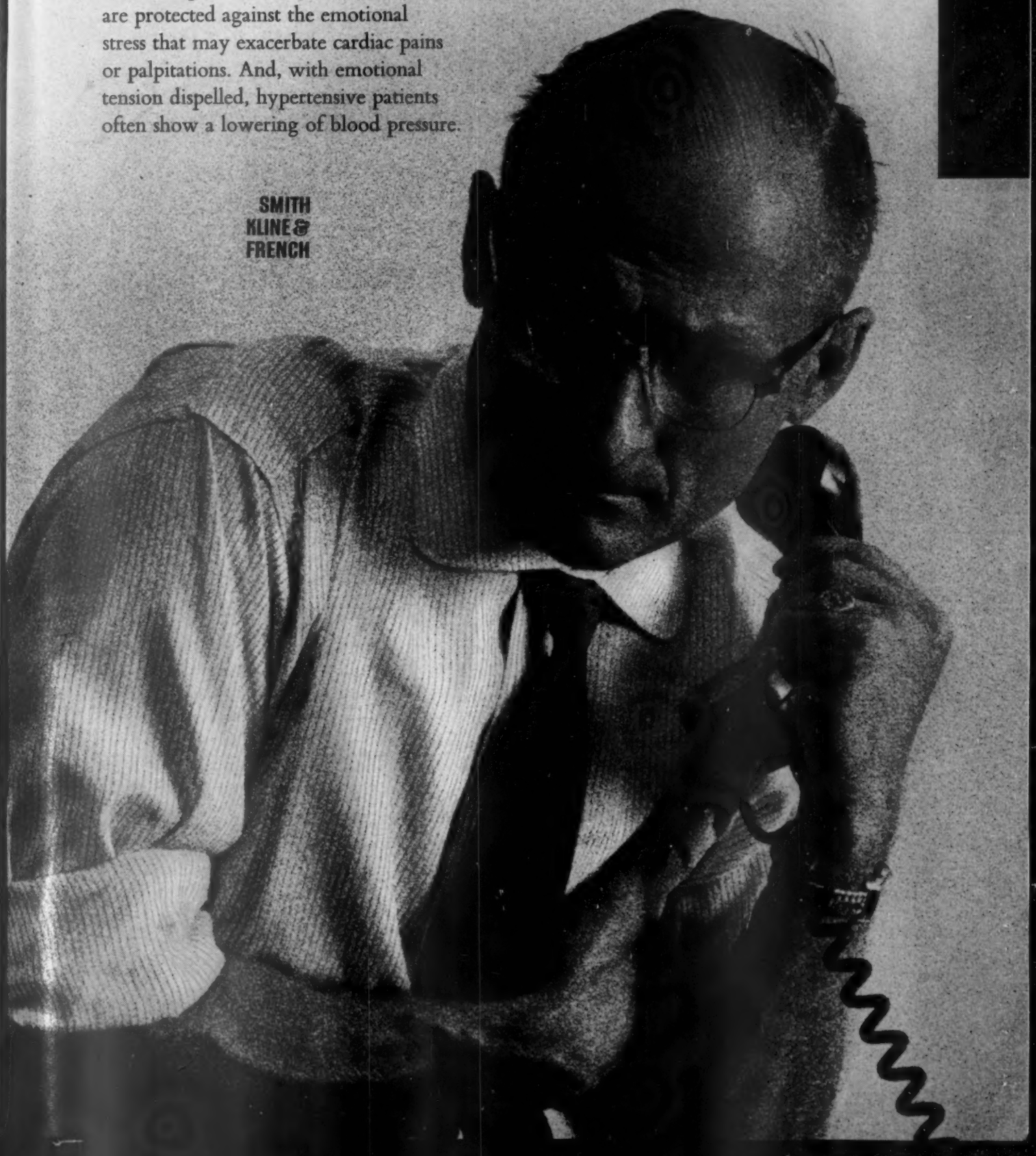

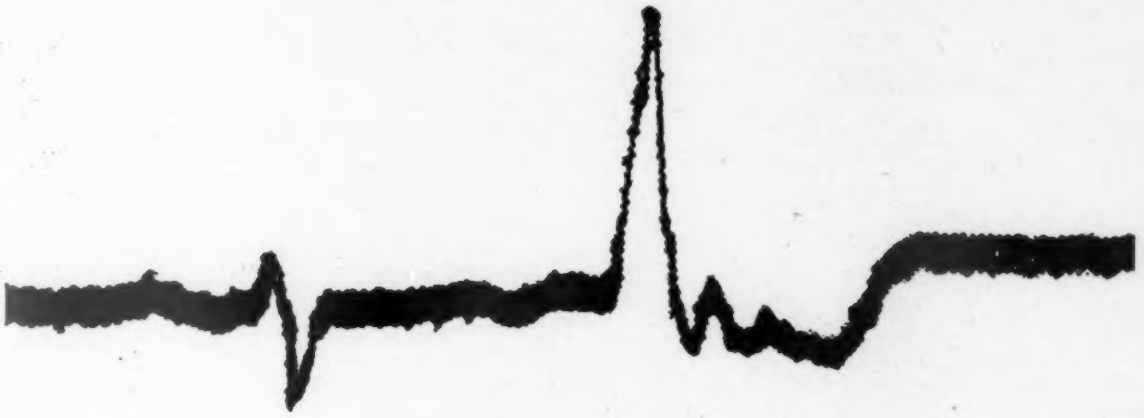

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References: 1. Zapata-Diaz, J., et al.: Am. Heart J. 43:854, 1952. 2. Modell, W.: In Drugs of Choice, C.V. Mosby Co., St. Louis, 1958, p. 454. 3. Kayden, H. J., et al.: Mod. Concepts Cardiovasc. Dis. 20:100. 1951. 4. Miller, H., et al.: J.A.M.A. 146:1004, 1951.

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safe and practical treatment of the postcoronary patient

A basic characteristic of the postcoronary patient, whether or not cholesterol levels are elevated, is his inability to clear fat from his blood stream as rapidly as the normal subject.[1-3] *Figure #1* graphically illustrates this difference in fat-clearing time by comparing atherosclerotic and normal subjects after a fat meal.[3]

"Slow clearers" gradually accumulate an excess of fat in the blood stream over a period of years as each meal adds an additional burden to an already fat-laden serum. As shown in *figure #2*, the blood literally becomes saturated with large fat particles, presenting a dual hazard to the atherosclerotic patient: the long-term danger of deposition of these fats on the vessel walls,[4] and the more immediate risk of high blood fat levels after a particularly heavy meal possibly precipitating acute coronary embarrassment.[5]

In *figure #3*, the test tube at the left contains lipemic serum, while the one at the right contains clear, or normal serum. If serum examined after a 12-hour fasting period presents a milky appearance, this is a strong indication that the patient clears fat slowly and is a candidate for antilipemic therapy in an effort to check a potentially serious situation.

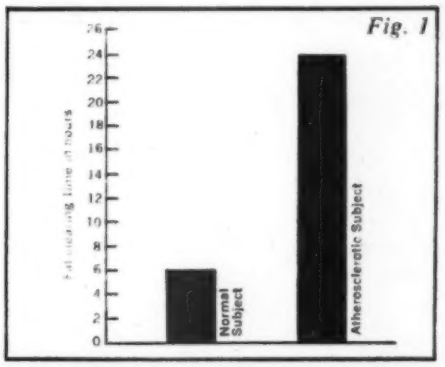
'Clarin', which is heparin in the form of a *sublingual tablet*, has been demonstrated to clear lipemic serum.[2,6,7] Furthermore, a two-year study using matched controls resulted in a statistically significant reduction of recurrent myocardial infarction in 130 patients treated with 'Clarin'.[8]

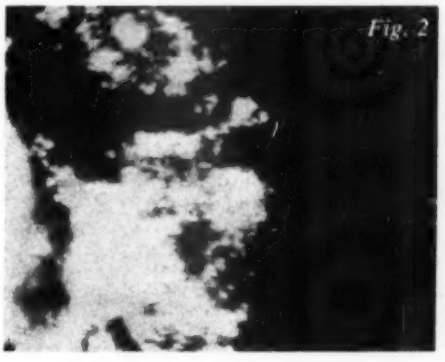
'Clarin' therapy is simple and safe, requiring no clotting-time or prothrombin determinations. Complete literature is available to physicians upon request.

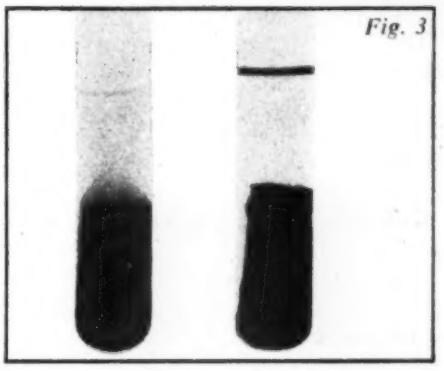
References: 1. Anfinsen, C. B.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council Publication 338, 1955, p. 218. 2. Berkowitz, D.; Likoff, W., and Spitzer, J. J.: Clin. Res. 7:225 (Apr.) 1959. 3. Stutman, L. J., and George, M.: Clin. Res. 7:225 (Apr.) 1959. 4. Wilkinson, C. F., Jr.: Annals of Int. Med. 45:674 (Oct.) 1956. 5. Kuo, P. T., and Joyner, C. R., Jr.: J.A.M.A. 163:727 (March 2) 1957. 6. Fuller, H. L.: Angiology 9:311 (Oct.) 1958. 7. Shaftel, H. E., and Selman, D.: Angiology 10:131 (June) 1959. 8. Fuller, H. L.: Circulation 20:699 (Oct.) 1959.

Clarin*

(sublingual heparin potassium, Leeming)







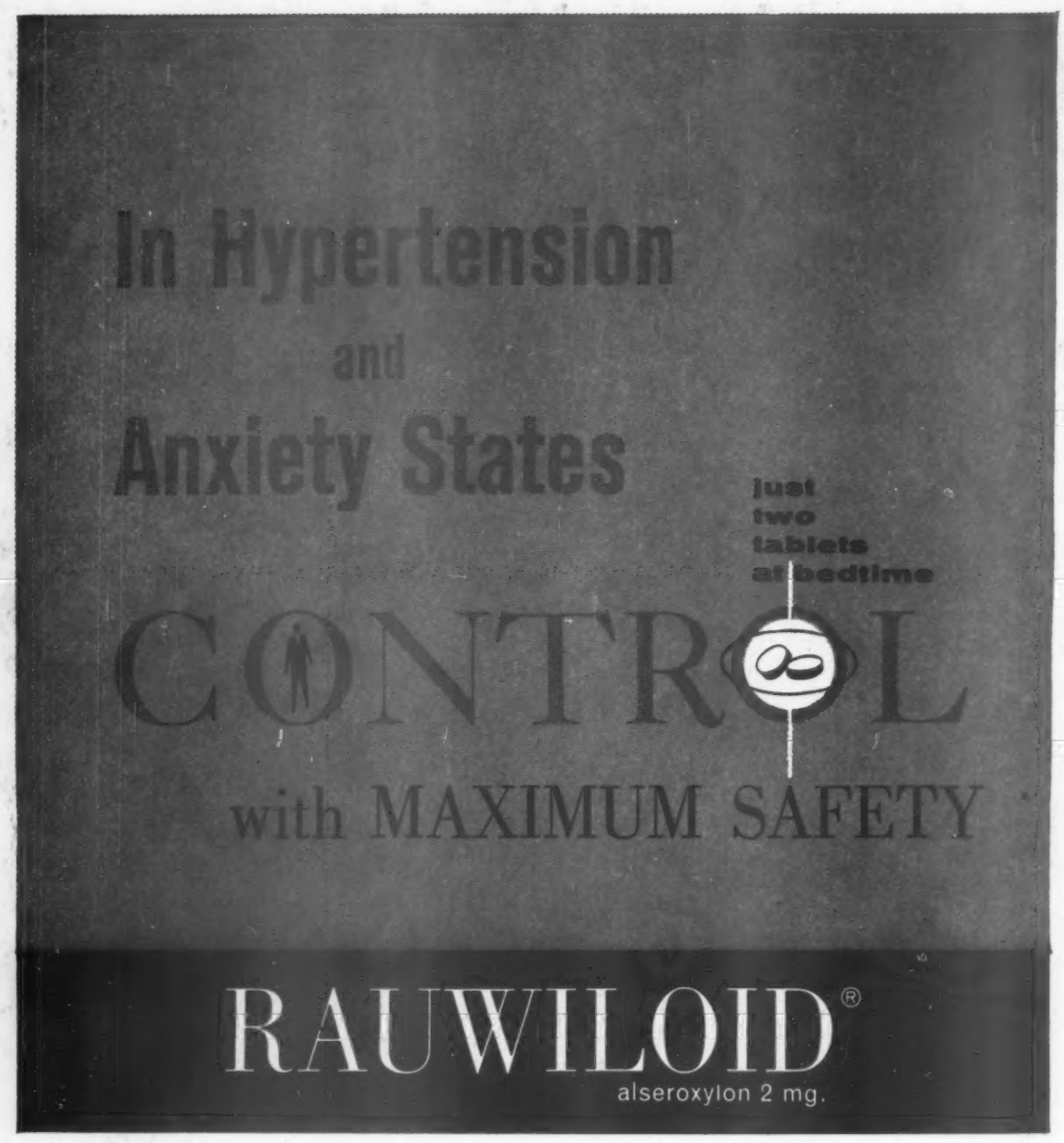
Indication: For the management of hyperlipemia associated with atherosclerosis, especially in the postcoronary patient.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: 'Clarin' is supplied in bottles of 50 pink, sublingual tablets, each containing 1500 I.U. of heparin potassium.

*Registered trade mark. Patent applied for.

Thos. Leeming & Co., Inc.
New York 17, N. Y.



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